VIA HAND CARRY
Date: February 10, 2011
Attorney Docket No.: P0035179.01

35 USC 156 Patent Term Extension Petition
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 6,575,966 B2
Issued: June 10, 2003
Assignee: Medtronic CryoCath LP

Atty. Docket: P0035179.01 (21819-169)

For: **Endovascular Cryotreatment Catheter**

Application for Extension of Patent Term Under 35 U.S.C. § 156

Sir:

The application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and two (2) copies thereof.

Enclosed herewith are the following documents:

☒ Application for Extension of Patent Term Under 35 U.S.C. § 156

☒ Attachment A – Food and Drug Administration (FDA) Technical Manual

☒ Attachment B - Device Description section of the Pre-Market Approval Application (PMA) submitted to the FDA on March 12, 2010;

☒ Attachment C – December 17, 2010 Approval Letter from FDA

☒ Attachment D – US Patent No. US 6,575,966 B2;

☒ Attachment E - Maintenance fee statements indicating payment of the maintenance fees in 2006 and 2010 ;

☒ Attachment F – August 28, 2003 letter from the FDA Center for Devices and Radiological Health;

☒ Attachment G – May 25, 2005 FDA full approval Letter;

☒ Attachment H – March 12, 2010 FDA letter to Milder acknowledging receipt of PMA;

☒ Attachment I - Chronology of Events on Arctic Front® device;

☒ Form PTO-2038 – Credit Card Payment Form;

☒ The Commissioner is hereby authorized to charge payment of any additional filing fees or credit any overpayment under §1.16 associated with this communication to Deposit Account No. 502104.

04/13/2011 KLOGAN 00000005 07943319
01 FC:1457 1120.00 OP

JOHN CHRISTOPHER
Reg. No. 37,596
Attorney for Applicant
Customer No.: 89554
Telephone: (954) 828-1488

Christopher & Weisberg, P.A.
200 East Las Olas Boulevard – Suite 2040
Ft. Lauderdale, Florida 33301
268857

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 6,575,966 B2
Issued: June 10, 2003
Assignee: Medtronic CryoCath LP

For: **Endovascular Cryotreatment Catheter**

Atty. Docket: P0035179.01

Application for Extension of Patent Term Under 35 U.S.C. § 156

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Mail Stop Hatch-Waxman PTE

Sir:

Your Applicant, **Medtronic CryoCath LP**, represents that it is the assignee of the entire interest in and to Letters Patent of the U.S. Patent No. 6,575,966 B2 granted to Miriam Lane, Leonilda Capuano, David Holtan, Jean-Pierre Lalonde, Claudia Lückge, Jean-Luc Pageard, Marwan Abboud, Johnny Al Asmar, Abderrahim Benrabah, Ken Chen, John W. Lehmann, Philippe Marchand, Robert Martin, Fredric L. Milder, and Daniel Nahon on the 10th day of June, 2003, for **Endovascular Cryotreatment Catheter** by virtue of 1) an Assignment from the inventors to CryoCath Technologies Inc. recorded February 12, 2002, Reel 012630, Frame 0146; and 2) an Assignment from CryoCath Technologies Inc. to **Medtronic CryoCath LP** recorded August 20, 2009, Reel 023119, Frame 0651.

Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the

convenience of the Patent and Trademark Office, the information contained in this application is presented in a format which follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved product comprises an Arctic Front CryoCatheter System identified by tradename as the "Arctic Front® Cardiac CryoAblation Catheter System" (hereafter "the Arctic Front® device").

The Arctic Front® device is a medical device for the treatment of patients with drug refractory recurrent symptomatic paroxysmal atrial fibrillation (PAF). The device is intended to reduce subsequent occurrence of symptomatic atrial fibrillation. The system produces controlled cryogenic temperatures to treat arrhythmias in a minimally invasive, precise, percutaneous manner. The system includes three major components: an Arctic Front Cardiac Cryoablation Catheter, a CryoConsole, and related components. The Cryoablation catheter is a flexible over-the-wire balloon catheter used to ablate cardiac tissue. It reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the balloon segment. A thermocouple positioned inside the balloon provides temperature reading capability. The catheter is introduced into the vasculature by traditional minimally invasive techniques. The Arctic Front Cryoablation Catheter is available in two models: 2AF232 (23 mm inflated balloon diameter) and 2AF282 (28 mm inflated balloon diameter). A copy of the Food and Drug Administration (FDA) Technical Manual is attached as Attachment A. A copy of the Device Description section of the Pre-Market Approval Application (PMA) submitted to the FDA on March 12, 2010 is attached as Attachment B.

(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 515.

(3) The approved product received permission for commercial marketing or use under Section 515 of the Federal Food, Drug and Cosmetic Act on **December 17, 2010**. A copy of the approval letter is attached as Attachment C.

(4) This subsection is not applicable to medical devices.

(5) The application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period will expire on **February 14, 2011**.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Miriam Lane, Leonilda Capuano, David Holtan, Jean-Pierre Lalonde, Claudia Lückge, Jean-Luc Pageard, Marwan Abboud, Johnny Al Asmar, Abderrahim Benrabah, Ken Chen, John W. Lehmann, Philippe Marchand, Robert Martin, Fredric L. Milder, and Daniel Nahon

Patent No.: US 6,575,966 B2

Issue Date: June 10, 2003

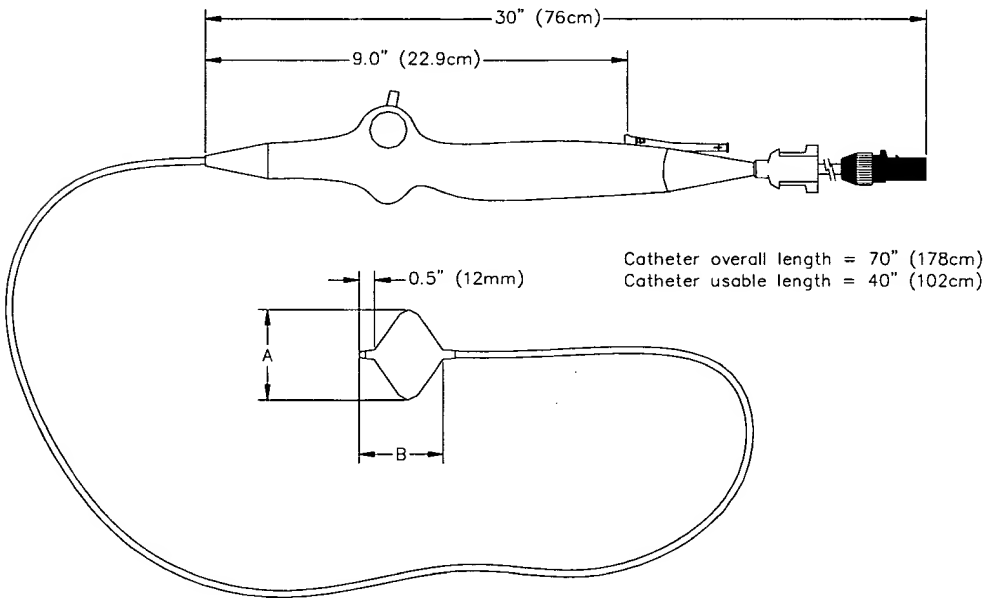
Expiration Date: August 23, 2019 (i.e., 20 years from its earliest effective date)

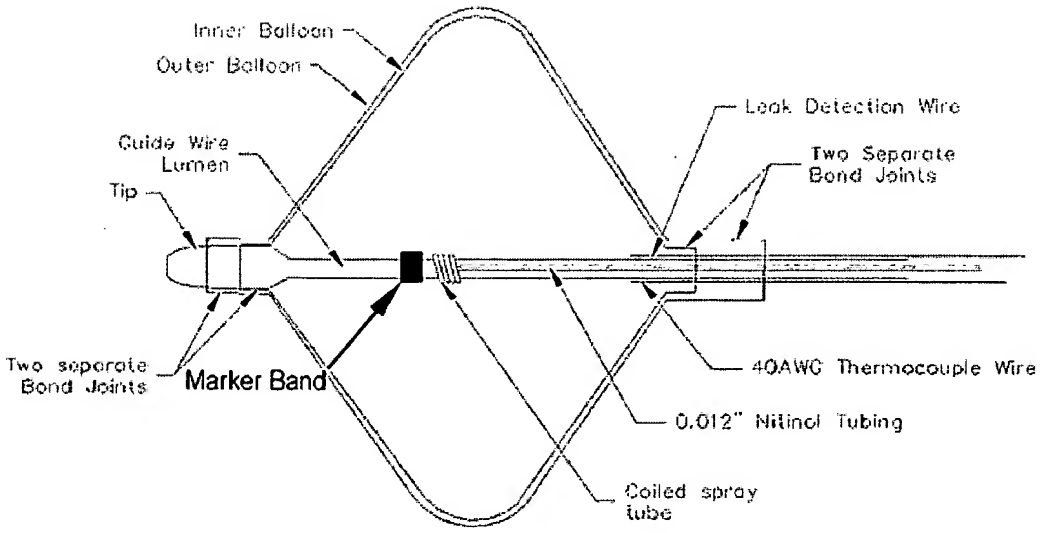
U.S. Patent No. 6,575,966 B2 is a continuation-in-part of U.S. Patent Application No. 09/378,972, filed on August 23, 1999, now U.S. Patent No. 6,283,959.

(7) A true copy of the patent is attached (Attachment D).

(8) No Terminal Disclaimer or Reexamination Certificate has been issued on this patent. No Certificate of Correction has been issued on this patent. Enclosed are copies of the maintenance fee statements indicating payment of the maintenance fees in 2006 and 2010 (Attachment E).

(9) U.S. Patent No. 6,575,966 B2 covers the Arctic Front® device in the following applicable claim (see Table 1 below). Portions of the Arctic Front® device are shown in the below figures.





The approved Arctic Front® device is within the scope of at least claims 1, 2, 13, and 15-19 of U.S. Patent No. 6,575,966 B2. For convenience, set forth below in Table 1 is a comparison of the limitations of exemplary claims 1, 2, 13, and 15-19 and the Arctic Front® device.

Table 1

Claim 1	Arctic Front® device
A catheter comprising: an elongate catheter body,	As seen in the above figures, the Arctic Front® device includes a catheter having an elongate catheter body.
cooling chamber defined within the catheter body,	The Arctic Front® device includes a cooling chamber (seen in the above figures) inside the inner balloon.
an expandable member disposed around the cooling chamber to define an interstitial space therebetween;	The Arctic Front® device includes an expandable member (the outer balloon) disposed around the cooling chamber to define an interstitial space therebetween.
wherein the cooling chamber is a first expandable membrane inflatable from a first state to a second state;	The cooling chamber of the Arctic Front® device is an expandable membrane (inner balloon) that is inflatable form a first state to a second state.
wherein the catheter body further	The Arctic Front® device includes a

comprises a coolant injection tube in fluid communication with: (i) a source of coolant, and (ii) the cooling chamber, and	coolant injection tube in fluid communication with the CryoConsole portion of the device, which is a source of coolant. The coolant injection tube is also in fluid communication with the cooling chamber formed by the inner balloon.
wherein the cooling chamber is inflatable by the flow of coolant from the injection tube into the first expandable membrane;	The inner balloon of the Arctic Front® device is inflatable by flow of a coolant from the coolant injection tube into the inner balloon.
wherein the catheter body further comprises a primary coolant return lumen in fluid communication with: (i) a source of fluid evacuation, and (ii) the cooling chamber, and	The catheter of the Arctic Front® device includes a primary coolant return lumen (the inner lumen of the catheter) that is in fluid communication with the interior of the cooling chamber and the CryoConsole portion of the device, which serves as a fluid evacuation source.
wherein the coolant injection tube, the cooling chamber, and the primary coolant return lumen define a first fluid pathway for the flow of coolant; and	The coolant injection tube, the interior of the inner balloon, and the coolant return lumen define a first fluid pathway for the flow of coolant.
wherein the catheter body further comprises a secondary coolant return lumen in fluid communication with: (i) a source of fluid evacuation, and (ii) the interstitial space, and	The catheter of the Arctic Front® device includes a secondary coolant return lumen (an outer lumen) that is in fluid communication and the CryoConsole portion of the device, which serves as a fluid evacuation source.
wherein the interstitial space and the secondary coolant return lumen define a second fluid pathway for the flow of coolant.	The interstitial space between the inner balloon and the outer balloon and the second coolant return lumen define a second fluid pathway for the flow of coolant.
Claim 2	Arctic Front® device
The catheter of claim 1, wherein the cooling chamber has an outer surface and the expandable member has an inner surface, said surfaces being substantially in apposition to one another to define a first volume of the interstitial space.	The interior of the inner balloon of the Arctic Front® device has an outer surface and the outer balloon of the Arctic Front® device has an inner surface. The surfaces are substantially in opposition to one another to define a first volume of the interstitial space.
Claim 13	Arctic Front® device
The catheter of claim 1, further comprising at least one temperature	A temperature sensor is disposed within the cooling chamber of the Arctic

sensor disposed within the cooling chamber.	Front® device.
Claim 15	Arctic Front® device
A catheter comprising:	As seen in the above figures, the Arctic Front® device includes a catheter.
a handle	The Arctic Front® device includes a handle, as shown in the above figures.
in fluid communication with a supply of cooling fluid having a boiling temperature, and a source of fluid evacuation,	The handle is in fluid communication with the CryoConsole portion of the Arctic Front® device, which includes a supply of cooling fluid having a boiling temperature. The CryoConsole is also a source of fluid evacuation.
a cooling chamber having fluid impermeable inner and outer surfaces,	The Arctic Front® device includes a cooling chamber (seen in the above figures) inside the inner balloon. The inner and outer surfaces of the inner balloon are fluid impermeable.
an elongate catheter body having	The catheter of the Arctic Front® device includes an elongate catheter body.
a coolant injection lumen having proximal and distal end portions, the proximal end portion being in fluid communication with the supply of cooling fluid, the distal end portion being in fluid communication with the cooling chamber, and a primary return lumen having proximal and distal end portions, the proximal end portion being in fluid communication with the source of vacuum, the distal end portion being in fluid communication with the cooling chamber, and	The catheter of the Arctic Front® device includes a coolant injection lumen. A proximal end portion of the coolant injection lumen is in fluid communication with the CryoConsole portion of the device, which is a source of coolant. The distal end portion of the coolant injection lumen is in fluid communication with the cooling chamber formed by the inner balloon.
a primary return lumen having proximal and distal end portions, the proximal end portion being in fluid communication with the source of vacuum, the distal end portion being in fluid communication with the cooling chamber,	The Arctic Front® device includes a primary return lumen. A proximal end portion of the primary return lumen is in fluid communication with the CryoConsole, which is a source of vacuum. A distal end of the primary return lumen is in fluid communication with the cooling chamber.
an expandable member having inner and outer surfaces coupled around said cooling chamber, wherein a space exists between the cooling	The Arctic Front® device includes an expandable member (the outer balloon) having inner and outer surfaces. The outer balloon is coupled around the

chamber outer surface and the expandable member inner surface, and	inner balloon to define a space between the outer surface of the inner balloon and the inner surface of the outer balloon.
a secondary return lumen disposed within the catheter body, having proximal and distal end portions, the proximal end portion being in fluid communication with the source of vacuum, the distal end portion being in fluid communication with the space.	The catheter of the Arctic Front® device includes a secondary coolant return lumen (an outer lumen) disposed within the catheter body. The secondary coolant return lumen has a proximal end portion in fluid communication with the CryoConsole portion of the device, which serves as a vacuum source. The secondary coolant return lumen also has a distal end that is in fluid communication with the space between the inner and outer balloons.
Claim 16	Arctic Front® device
The catheter of claim 15, wherein the cooling chamber is controllably filled with cooling fluid, and vacuum is applied to the primary return lumen to direct the cooling fluid to flow from the cooling chamber through to the primary return lumen.	In use, the inner balloon of the Arctic Front® device is controllably filled with cooling fluid, and a vacuum is applied to the primary return lumen to direct the cooling fluid to flow from the cooling chamber through to the primary return lumen.
Claim 17	Arctic Front® device
The catheter of claim 16, wherein the outer surface of the expandable member is disposed in contact with tissue proximate a body lumen to effect thermal conduction between said tissue and the flow of cooling fluid in the cooling chamber.	In use, the outer surface of the outer balloon of the Arctic Front® device is disposed in contact with tissue proximate a body lumen to effect thermal conduction between said tissue and the flow of cooling fluid in the cooling chamber.
Claim 18	Arctic Front® device
The catheter of claim 16, wherein vacuum is applied to the secondary return lumen.	In use, a vacuum is applied to the secondary return lumen of the Arctic Front® device.
Claim 19	Arctic Front® device
The catheter of claim 15, wherein the cooling chamber is an inflatable membrane transitionable from a first volume to a second volume, the second volume being larger than the first volume.	The inner balloon of the Arctic Front® device is an inflatable membrane that is transitionable from a first volume to a second volume, the second volume being larger than the first volume.

(10)(v) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(A) Investigational Device Exemption (IDE) application for the Arctic Front® device was filed on August 1, 2003 and became effective on **August 28, 2003** as a conditional approval (G030159). A copy of the letter from the FDA Center for Devices and Radiological Health substantiating this date is attached as Attachment F. The full approval for IDE G030159 was granted by the FDA on May 25, 2005 (Attachment G).

(B) PMA application for the Arctic Front® device was submitted as a modular submission (M080006), wherein the first module was submitted on July 30, 2008. The last module (i.e., the 4th module) of the PMA application was submitted on **March 12, 2010** and the PMA number P100010 was assigned. A copy of the letter from the FDA substantiating this date is attached as Attachment H.

(C) PMA P100010 for the Arctic Front® device was approved on **December 17, 2010** (Attachment C).

(11) A brief description of significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the Arctic Front® device and the dates applicable to these significant activities are set forth in a chronology of events in Attachment I.

(12)(i) Applicant is of the opinion that U.S. Patent No. 6,575,966 B2 is eligible for extension of the patent term under 35 U.S.C. § 156 because it satisfies all requirements for such extension as follows:

(a) 35 U.S.C. § 156(a) - U.S. Patent No. 6,575,966 B2 claims a product, which is the Arctic Front® device.

(b) 35 U.S.C. § 156(a)(1) - U.S. Patent No. 6,575,966 B2 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2) - The term of U.S. Patent No. 6,575,966 B2 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4) - The Arctic Front® device has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The commercial marketing or use of the Arctic Front® device after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (i.e., Section 515) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4) - No other patent has been extended for the same regulatory review period for the Arctic Front® device.

(12)(ii) The length of the extension of patent term of U.S. Patent No. 6,575,966 B2 claimed by Applicant is that period authorized by 35 U.S.C. § 156(c)

which has been calculated to be **1476** days. The length of the extension was determined pursuant to 37 C.F.R. § 1.777 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on **August 28, 2003** and ended **December 17, 2010**, which is a total of **2670** days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period," began on **August 28, 2003** and ended on **March 12, 2010**, which is **2389** days; and

(2) The period of review under 35 U.S.C. § 156 (g)(1)(B)(ii), the "Approval Period," began on **March 12, 2010**, and ended on **December 17, 2010**, which is a total of **281** days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (**2670** days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (June 10, 2003) which is zero (0) days; and

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

(3) One-half the number of days determined in sub-paragraph (12)(ii)(a)(1) above after the patent issued (one-half of **2389** days) which is **1194** days;

(c) The number of days as determined in sub-paragraph (12)(ii)(b) (**1476** days) when added to the expiration date of the original term of the patent (August 23, 2019) would result in the date of **September 7, 2023**;

(d) Fourteen (14) years when added to the date of the PMA approval (December 17, 2010) would result in the date of **December 17, 2024**;

(e) The earlier date as determined in sub-paragraphs (12)(ii)(c) and (12)(ii)(d) is **September 7, 2023**;

(f) Since U.S. Patent 6,575,966 B2 issued after September 24, 1984, the period of extension may not exceed five (5) years from the original expiration date of August 23, 2019. Five years when added to the original expiration date of the patent would result in the date of **August 23, 2024**.

(g) The earlier dates as determined by sub-paragraph (12)(ii)(e) and (12)(ii)(f) is **September 7, 2023**.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon this application is attached in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 502104.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

John Christopher

Christopher & Weisberg, P.A.

200 East Las Olas Boulevard

Suite 2040

Fort Lauderdale, FL 33301

Phone: (954) 828-1488

Fax: (954) 828-9122

(16) The application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and two (2) copies thereof.

Respectfully submitted,

CHRISTOPHER & WEISBERG, P.A.

By: _____

John Christopher
Attorney for Applicant
Registration No. 37596
Customer No. 89554

Date: February 10, 2011

200 East Las Olas Boulevard
Suite 2040
Fort Lauderdale, FL 33301
Tel: (954) 828-1488
Fax: (954) 828-9122
Email: ptomail@cwiplaw.com

268859

Medtronic

ARCTIC FRONT®
2AF232, 2AF282

Cardiac CryoAblation Catheter

Technical Manual

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

The following are trademarks or registered trademarks of Medtronic in the United States and possibly in other countries: Arctic Front, FlexCath, Medtronic

Explanation of symbols

Refer to the package labels to see which of the following symbols apply to this product

LOT	Lot number
REF	Reorder number
	Use by
STERILE EO	Sterilized using ethylene oxide
	Do not reuse
	Do not resterilize
	Do not use if package is damaged
	Package contents
	Consult instructions for use
	Fragile: handle with care
	Keep dry
	Product documentation
	Temperature limitation
	Do not freeze
	Cardiac cryoablation catheter
	Open here
! USA	For US audiences only

1 Description

The Arctic Front Cardiac CryoAblation Catheter (Arctic Front Cryoballoon) is a flexible, over-the-wire balloon catheter used to ablate cardiac tissue. It is used together with the FlexCath Steerable Sheath, the CryoConsole, and related components. The balloon reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the balloon segment. A thermocouple positioned inside the balloon provides temperature reading capability. The catheter is introduced into the vasculature by traditional minimally invasive techniques. The Arctic Front Cryoballoon is available in 2 models, as described in the following table:

Model	Inflated balloon diameter
2AF232	23 mm
2AF282	28 mm

For details about the CryoConsole and how to use it with the catheter to perform cryoablation procedures, see the *CryoConsole Operator' Manual.*

1.1 Contents of package

The catheter is supplied sterile. The package contains the following items:

- 1 Arctic Front Cardiac CryoAblation Catheter
- product documentation

2 Indications for use

The Arctic Front Cardiac CryoAblation Catheter is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

3 Contraindications

Use of the Arctic Front Cardiac CryoAblation Catheter is contraindicated as follows:

- in the ventricle because of the danger of catheter entrapment in the chordae tendineae
- in patients with active systemic infections
- in conditions where the manipulation of the catheter within the heart would be unsafe (for example, intracardiac mural thrombus)
- in patients with cryoglobulinemia
- in patients with one or more pulmonary vein stents

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures. Administer anticoagulation therapy during and post-procedure according to the institutions standards. The Arctic Front Cardiac CryoAblation Catheter was not studied for the safety of changes in anticoagulation therapy in patients with paroxysmal atrial fibrillation.

Balloon inflation/deflation – If the balloon cannot be inflated or deflated using the CryoConsole, have a Manual Retraction Kit on hand during the procedure. (Refer to the operators manual for more detailed instructions on the Manual Retraction Kit).

- Do not inflate the balloon inside the sheath. Always verify with fluoroscopy that the balloon is fully outside the sheath before inflation to avoid catheter damage.
- Do not inflate the balloon while the catheter is positioned inside a pulmonary vein. Always inflate the balloon in the atrium and then position it at the pulmonary vein ostium. Inflating the balloon in the pulmonary vein may result in vascular injury.

Biohazard disposal – Discard all used catheters and sterile components in accordance with hospital procedures.

Cardioversion/defibrillation during ablation procedure – Disconnect the catheters electrical connection prior to cardioversion/defibrillation. Failure to do so may trigger system messages indicating a need for catheter exchange.

Catheter handling –

- Use extreme care when manipulating the catheter. Lack of careful attention can result in injury such as perforation or tamponade.
- Do not use excessive force to advance or withdraw the catheter, especially if resistance is encountered.
- Do not use the catheter if it is kinked, damaged, or cannot be straightened.
- Straighten the cooling segment before inserting or withdrawing the catheter.
- Do not at any time preshape or bend the catheter shaft or cooling segment. Bending or kinking the catheter shaft may damage internal structures and increase the risk of catheter failure. Prebending of the distal curve can damage the catheter.
- Catheter advancement should be performed under fluoroscopic guidance.
- The catheter should be replaced if a System Notice (message on the CryoConsole user interface) recommends it.
- Do not position the cryoballoon catheter within the tubular portion of the pulmonary vein to minimize phrenic nerve injury and pulmonary vein stenosis.

Catheter integrity – Do not use the catheter if it is kinked or damaged. If the catheter becomes kinked or damaged while in the patient, remove it and use a new catheter. Prior to injecting, the physician should ensure that there is no kink in the catheter.

Correct guide wire insertion and positioning – Do not advance the balloon beyond the guide wire to reduce the risk of tissue damage.

- Ensure the guide wire is inserted into the catheter and through the balloon portion for adequate support during vascular access insertion. Failure to do so may result in catheter damage.

Cryoablation near prosthetic heart valves – Do not pass the catheter through a prosthetic heart valve (mechanical or tissue). The catheter may become trapped in the valve, damaging the valve and causing valvular insufficiency or premature failure of the prosthetic valve.

Cryoadhesion – Do not pull on the catheter, sheath, umbilical cables, or console while the catheter is frozen to the tissue, as this may lead to tissue injury.

Do not resterilize – Do not resterilize this device for purpose of reuse. Resterilization may compromise the structural integrity of the device or create a risk of contamination from the device that could result in patient injury, illness, or death.

Embolism risk – Introducing any catheter into the circulatory system entails the risk of air or gas embolism, which can occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism.

Environmental limits – Perform cryoablation procedures only within the environmental parameters. Operating outside these parameters may prevent the start or completion of a cryoablation procedure. Refer to the Specifications Table on page page 12 for environmental parameters.

Fluid incursion – Do not expose the catheter handle or coaxial and electrical connectors to fluids or solvents. If these components get wet, the Arctic Front Cryoballoon may not function properly, and connector integrity may be compromised.

Fluoroscopy required for catheter placement – The use of fluoroscopy during catheter ablation procedures presents the potential for significant x-ray exposure to both patients and laboratory staff. Extensive exposure can result in acute radiation injury and increased risk for somatic and genetic effects. Only perform catheter ablation after giving adequate attention to the potential radiation exposure associated with the procedure, and taking steps to minimize this exposure. Give careful consideration before using the device in pregnant women.

For single use only – This device is intended only to be used once for a single patient. Do not reuse, reprocess, or resterilize this device for purpose of reuse. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device or create a risk of contamination of the device that could result in patient injury, illness, or death.

Frequent flushing of the guide wire lumen – Flush the guide wire lumen initially and then to prevent coagulation of blood in the lumen. Flush the guide wire lumen with saline after each contrast injection.

Improper connection – Do not connect the cryoablation catheter to a radiofrequency (RF) generator or use it to deliver RF energy. Doing this may cause catheter malfunction or patient harm.

Induced arrhythmias – Catheter procedures may mechanically induce arrhythmias.

Leakage current from connected devices – Use only isolated equipment (IEC 60601-1 Type CF equipment, or equivalent) with the CryoConsole and catheters or patient injury or death may occur.

Other catheters, devices, or wires – Avoid catheter entanglement with other catheters, devices, or wires. Such entanglement may necessitate surgical intervention.

Phrenic nerve impairment – Stop ablation immediately if phrenic nerve impairment is observed. Use continuous phrenic nerve pacing throughout each cryoablation application in the right pulmonary veins. To avoid nerve injury, place a hand on the abdomen, in the location of the diaphragm to assess for changes in the strength of the diaphragmatic contraction or loss of capture. In case of no phrenic nerve capture, frequently monitor diaphragmatic movement using fluoroscopy. Position the balloon as antral as possible and not in the tubular portion of the pulmonary vein. New onset hemi-diaphragmatic movement disorder, detected by radiologic assessment, was observed in 11.2% (29/259) of all cryoablation procedures (See Section 5.8.4 for study results).

Post-ablation period – Closely monitor patients undergoing cardiac ablation procedures during the post-ablation period for clinical adverse events.

Pressurized refrigerant – The catheter contains pressurized refrigerant during operation. Release of this gas into the circulatory system due to equipment failure or misuse could result in gas embolism.

Pulmonary vein narrowing or stenosis – Catheter ablation procedures inside or near pulmonary veins may induce pulmonary vein narrowing and/or stenosis. Do not ablate in the tubular portion of the pulmonary vein. The occurrence of this complication may necessitate percutaneous angioplasty or surgical intervention. Seven of 228 (3.1%) cryoablated study subjects had one or more stenosed pulmonary veins (PV's) detected during study imaging (See Section 5.8.3 for study results.)

Required use environment – Cryoablation procedures should be performed only in a fully equipped facility.

RF ablation – Before powering up an RF generator or applying RF energy, disconnect the cryoablation catheter from the CryoConsole to avoid a System Notice message and unnecessary catheter replacement.

Septal damage – Always deflate the balloon and withdraw it into the transseptal sheath before removing it from the left atrium. Crossing the septum while the balloon is unsheathed, inflated, or inflating in the septal puncture site may cause serious septal damage.

Steerable sheath compatibility – Use only the 12 Fr FlexCath Steerable Sheath with the Arctic Front Cardiac CryoAblation Catheter. Using another sheath may damage the catheter or balloon segment.

Sterile package inspection – Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter is damaged, do not use the catheter. Contact your Medtronic representative.

System compatibility – Use only Medtronic cryoablation catheters, refrigerant tanks, and components with the CryoConsole. The safety and use of other catheters or components has not been tested.

Qualified users – This equipment should be used only by or under the supervision of physicians trained in left atrial cryoablation procedures.

5 Clinical summary

Study title:	STOP-AF: A Randomized, Controlled Clinical Trial of Catheter Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation
Number of centers:	26 centers in the United States and Canada
Number of subjects:	245 randomized subjects

5.1 Study purpose

To evaluate the safety and effectiveness of the Arctic Front Cardiac Cryoablation Catheter System, including the FlexCath Steerable Sheath, Freezor MAX Cardiac Cryoablation Catheter, and CryoConsole (Gen V) in adult patients with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation drugs.

5.2 Study scope, design and methods

The study was a prospective, randomized, controlled, multicenter, pivotal clinical investigation conducted at 26 investigational sites (23 in the United States and 3 in Canada). Subjects with paroxysmal atrial fibrillation (PAF) referred for ablative intervention after efficacy failure of one or more Study Atrial Fibrillation (AF) Drugs (flecainide, propafenone, or sotalol) (Amiodarone was not considered a study AF Drug) were randomized 2:1 to cryoablation intervention (Experimental Subjects, ES) or to a Study AF Drug (Control Subjects, CS). Subjects were followed for 12 months with scheduled and symptom-driven assessments to detect recurrent atrial fibrillation by means of periodic electrocardiograms, weekly scheduled trans-telephonic monitoring, patient-initiated trans-telephonic monitoring, and 24-hour Holter monitoring at 6 and 12 months. The first 90 days after study therapy was initiated was considered a blanked period for all subjects.

5.3 Study endpoints

The primary effectiveness outcome was Treatment Success, defined on the basis of Chronic Treatment Failure events and the occurrence of Acute Procedural Success.

- **Treatment Success:** (TS), defined for CS as freedom from any Chronic Treatment Failure events, and for ES as both Acute Procedural Success **and** freedom from Chronic Treatment Failure from Day 0 through the 12 month follow-up visit. This comparison of proportions was to be performed using a 2-sided Fisher's Exact Test of binomial proportions with $a = 0.05$ and $b = 0.20$, with an estimate of TS in the groups of 40% Control and 60% Experimental and a 2:1 randomization, giving a sample size calculation of 240 evaluable subjects.
  - **Acute Procedural Success:** (APS), defined as the electrical isolation of ≥ 3 pulmonary veins from the left atrium (as reported after the first procedure) was an additional primary effectiveness outcome measure, for ES only.
  - **Chronic Treatment Failure:** (CTF), defined as Detectable AF (during the Non Blanked Follow-up Period), the use of Non Study AF Drugs, or an AF Intervention (Day 0 through the 12 month follow-up).

The initial cryoablation treatment date or the first day of AF Drug therapy was considered the Start Date for all subjects. Subjects were then followed for 12 months from their Start Date with scheduled and symptom-driven assessments to detect recurrent AF (Detectable AF) by means of periodic electrocardiograms (ECG), weekly scheduled transtelephonic monitoring (TTM), subject-initiated TTMs, and 24-hour Holter monitoring at 6- and 12- months. The 90 day interval following the Start Date was considered a Blanked Follow-up Period for all subjects. It was during this time period that the Control Subjects underwent AF Drug optimization and that Experimental Subjects were allowed one repeat cryoablation as needed. Occurrences of AF during the Blanked Follow-up Period were not considered as Chronic Treatment Failure (CTF) and did not count as an event against the primary objective. Control Subjects were allowed one crossover cryoablation treatment only after they demonstrated CTF. All repeat and crossover cryoablations required review and approval by the Medical Monitor or Principal Investigator.

The primary safety outcomes were Cryoablation Procedure Events and Major Atrial Fibrillation Events.

- **Cryoablation Procedure Events:** (CPE) defined for ES only as specifically categorized device- or procedure-related serious adverse events (SAE) with onset within 7 days of cryoablation (access site complications, cardiac damage, embolic complications, arrhythmias, persistent phrenic nerve palsy, or death) or with onset at any time through 12 months of follow-up (pulmonary vein stenosis or atrio-esophageal fistula). (Table 1)

Table 1. Cryoablation Procedure Event Categories

Cryoablation Procedure Events (CPE)	With onset between Day 0 and:
Access site complications requiring • Transfusion of 3 or more units; or • Surgical intervention; or • Permanent loss of functional impairment	Day 7
Cardiac damage (including MI)	Day 7
• Pulmonary vein stenosis	12-month follow-up visit*
• Atrio-esophageal fistula	12-month follow-up visit*
Embolic complications (including stroke)	Day 7
Arrhythmias	Day 7
Persistent phrenic nerve palsy	Day 7
Death	Day 7

*This CPE will be assessed through the completion of within window study follow-up.

- **Major Atrial Fibrillation Events:** (MAFE) defined for CS and ES as serious adverse events in the categories of cardiovascular death, myocardial infarction, stroke, or any hospitalization primarily related to AF recurrence/ablation, atrial flutter ablation (excluding Type I), systemic embolization, congestive heart failure, hemorrhagic event or anti-arrhythmic drug initiation, adjustment or complication. (Table 2)

Table 2. Major Atrial Fibrillation Events Categories

Major Atrial Fibrillation Events (MAFE)
Cardiovascular death
Myocardial infarction (MI)
Stroke
Associated with or leading to a hospitalization for (primary reason): • AF recurrence or ablation • Atrial flutter ablation (excluding Type I) • Systemic embolization (not stroke) • Congestive heart failure • Hemorrhagic event (not stroke) • Anti-arrhythmic drug initiation, adjustment, or complication

5.4 Subject accountability

Enrollment and accountability are summarized in the following table.

Table 3. Subjects accountability and disposition

Subject disposition	Control subjects	Experimental subjects	All subjects
Subjects provisionally enrolled and randomized	87	171	258
Screen failures	1	5	6
Withdrawal of consent	4	3	7
Subjects enrolled	82	163	245
Death	0	1	1
Lost to follow-up	0	0	0
Withdrawal of consent	3	0	3
Subjects completing 12 month follow-up	79	162	241
Control subjects crossing over to cryoablation	65	----	----
Experimental subjects undergoing reablation	----	31	----

Study populations for analysis were:

- Safety Population (n = 245): pre-specified, included all subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
- Effectiveness Populations
  - Modified intent-to-treat (n = 245): pre-specified included all subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
  - Per protocol Population (n = 181): pre-specified, included those subjects that received treatment in their randomized group and completed the Blanked Follow-up Period, having complete assessments for detection of AF through 12 months of follow-up including at least 80% compliance with rhythm monitoring, and having the absence of any major protocol violations.
- Cryoablated Control Population (n = 65): pre-specified, included those CS who underwent crossover cryoablation. Control subjects were allowed to undergo one cryoablation procedure under the protocol. All control subject crossovers were required to be approved by the Principal Investigator or Medical Monitor. Cryoablated control subjects were followed for 12 months from the date of the cryoablation procedure.
- Reablated Experimental Population (n = 31): pre-specified, included ES who underwent repeat cryoablation during the Blanked Follow-up Period. Experimental subjects were allowed to undergo an additional cryoablation procedure during the 90 day blanking period. Reablated experimental subjects maintained the same follow-up schedule as determined by initial study cryoablation procedure.

5.5 Subject demographics

The STOP AF study population consisted of mostly white ethnic background (94.3%), had a mean age of 56.6 years with 77.1% being male. The baseline characteristics were comparable between the randomized groups, as summarized in Table 4 and Table 5.

Table 4. Baseline demographics - age, echocardiography, AF symptoms, SF-36 score

	All subjects mean (SE) N median (min, max) N = 245	Control subjects mean (SE) N median (min, max) N = 82	Experimental subjects mean (SE) N median (min, max) N = 163	Difference [95% 95%C]*	p value
Age (years)	56.6 (0.60) 245 57.0 (26, 75)	56.4 (1.04) 82 56.5 (26, 72)	56.7 (0.73) 163 58.0 (33, 75)	0.3 [-2.2, 2.8]	0.797
Left atrial AP diameter (mm)	40.5 (5.4) 245 40 (24, 54)	40.9 (6.0) 82 40.5 (28, 54)	40.3 (5.1) 163 40 (24, 50)	-0.7 [-2.1, -0.8]	0.353
Left ventricular EF (%)	60.2 (5.6) 244 60 (40, 76)	60.7 (6.4) 82 60 (45, 76)	60.0 (5.7) 162 60 (40, 75)	-0.7 [-2.3, -0.9]	0.407
Symptomatic AF in the 2 months prior to enrollment	23.2 (2.54) 239 10.0 (2, 300)	21.2 (3.63) 80 10.0 (2, 250)	24.3 (3.36) 159 10.0 (2, 300)	3.0 [-7.6, 13.7]	0.540
Overall SF-36 score	70.63 (1.115) 231 74.0 (15.0, 98.0)	70.37 (1.716) 78 74.50 (29.0, 98.0)	70.76 (1.442) 153 74.00 (15.0, 98.0)	0.4% [-4.3, 5.0%]	0.870

* AP = Antero-posterior; EF = Ejection Fraction

Table 5. Baseline demographics - gender, ethnicity and NYHA Class

		All subjects % (n) N = 245	Control subjects % (n) N = 82	Experimental subjects % (n) N = 163	p value
Gender	Male	77.1% (189)	78.0% (64)	76.7% (125)	0.873
	Female	22.9% (56)	22.0% (18)	23.3% (38)	
Ethnicity	White	94.3% (231)	92.7% (76)	95.1% (155)	0.696
	Black	1.2% (3)	2.4% (2)	0.6% (1)	
	Hispanic	0.8% (2)	1.2% (1)	0.6% (1)	
	Asian	1.6% (4)	1.2% (1)	1.8% (3)	
	Other	2.0% (5)	2.4% (2)	1.8% (3)	
NYHA[a] Class	None / Class I	93.5% (229)	93.9% (77)	93.3% (152)	1.000
	Class II	6.5% (16)	6.1% (5)	6.7% (11)	
Cardio-vascular risk factors	Diabetes	7.3% (18)	8.5% (7)	6.7% (11)	0.612
	Hypertension	42.4% (104)	45.1% (37)	41.1% (67)	0.585
	Dyslipidemia	48.2% (118)	48.8% (40)	47.9% (78)	0.893

[a] NYHA = New York Heart Association

Previously failed AF Drugs for efficacy were comparable between study groups with 36% of all study subjects having failed flecainide, 47% having failed propafenone, and 29% having failed sotalol.

5.6 Results

5.6.1 Procedural data

The Arctic Front Cryocatheter parameters for first procedures in ES (n = 163) included approximately 3 cryoapplications for each of the 4 major pulmonary veins at a mean intra-catheter temperature between -48.6 and -54.1 °C, with a median duration of 240 seconds per cryoapplication (Table 6).

Table 6. Arctic Front Cryocatheter Cryoapplication Parameters by Pulmonary Vein Location, First Experimental Procedures (N = 163)

Cryoapplication parameters	RSPV[a] mean (SE) N median (min, max)	RIPV[a] mean (SE) N median (min, max)	LSPV[a] mean (SE) N median (min, max)	LIPV[a] mean (SE) N median (min, max)
# of cryo apps	2.9 (0.12) 161 3.0 (1, 11)	2.8 (0.14) 154 2.0 (0, 11)	3.6 (0.14) 150 3.0 (1, 12)	3.2 (0.11) 152 3.0 (1, 9)
Measured temp (°C)	-50.70 (0.73) 460 -51.0 (-80.0, 33.0)	-48.63 (1.00) 405 -48.0 (-81.0, 35.0)	-54.12 (0.79) 508 -55.0 (-81.0, 36.0)	-50.78 (0.78) 484 -49.0 (-81.0, 33.0)
Duration (secs)	196.9 (3.54) 473 240.0 (3, 240)	205.4 (3.69) 428 240.0 (3, 240)	219.3 (2.80) 534 240.0 (1, 240)	230.1 (2.07) 488 240.0 (4, 360)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The Freezor MAX Cryocatheter was used for gap cryoablations in a small proportion of major pulmonary veins during first experimental procedures (initial study cryoablation procedure). (Table 7)

Table 7. Freezor MAX Cryocatheter Use by Pulmonary Vein Location, First experimental procedures (N = 163)

Freezor MAX Cryocatheter Use	RSPV[a] % (n)	RIPV[a] % (n)	LSPV[a] % (n)	LIPV[a] % (n)
Experimental first procedures	4.9% (8)	9.2% (15)	4.3% (7)	4.3% (7)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The first experimental procedure lasted a mean of 371 minutes, with investigational devices inserted in the subject vasculature for a mean of 181 minutes. Cryoablation time averaged 65.7 minutes, and total fluoroscopy time averaged 62.8 minutes (Table 8).

Table 8. Cryoablation procedural durations, First experimental procedures (N = 163)

Procedure, Cryocatheter & fluoroscopy times	Total procedure duration mean (SE) N median (min, max)	Cryocatheter insertion time mean (SE) N median (min, max)	Total ablation time mean (SE) N median (min, max)	Total fluoroscopy time mean (SE) N median (min, max)
Experimental first procedures (min)	371.4 (7.89) 163 349.0 (200.0, 650.0)	181.2 (5.86) 162 169.0 (72.0, 427.0)	65.7 (2.70) 162 56.8 (17.0, 179.8)	62.8 (2.55) 162 54.0 (8.0, 229.0)

5.6.2 Compliance with follow-up and rhythm monitoring requirements

Follow-up compliance with key assessments was high, exceeding 90% in all cases except for Holter compliance which was as low as 72% at the 6 month follow-up visit in the Control group. The Holter monitoring assessment protocol requirements for cryoablated control subjects was reduced because cryoablated control subjects were considered chronic treatment failures. This meant further Holter monitoring was not required.

Pulmonary vein CT/MRI imaging was performed prior to a subjects first cryoablation procedure (Experimental and Cryoablated Control) as well as at 6 and 12 months post-cryoablation procedure for pulmonary vein stenosis surveillance (Table 9).

Table 9. Compliance with follow-up and monitoring requirements

Parameter		Control subjects%[a]	Experimental subjects%[b]	All subjects%[c]
Office visits	3 months	98.8%	100.0%	99.6%
	6 months	97.6%	100.0%	99.2%
	12 months	96.3%	99.4%	98.4%
Weekly TTMs		91.5%	91.5%	91.5%
Scheduled TTMs[d]		3,841	7,983	11,824
Unscheduled TTMs[d]		3,016	2,084	5,100
24° h Holter monitors	6 months[e]	72.8%	85.9%	81.6%
	12 months[f]	74.7%	88.9%	84.2%
Imaging of pulmonary veins	Baseline	100%	100%	100%
	6 months	95.4%	96.9%	96.5%
	12 months	93.8%	97.5%	96.4%

[a] Denominator = 82 except for imaging of pulmonary veins for which denominator = 65 cryoablated Control Subjects eligible for 6 month study and 47 eligible for 12 month study at time of report.
[b] Denominator = 163 Experimental Subjects.
[c] Denominator = 245 except for imaging of pulmonary veins for which denominator = 228 cryoablated subjects eligible for 6 month study and 205 eligible for 12 month study at time of report.
[d] Number of TTM recordings
[e] Has a holter recording between 150 and 210 days
[f] Has a holter recording between 335 and 395 days

5.6.3 Effectiveness outcomes and measures

The STOP AF trial defined three (3) Primary Effectiveness Outcome Measures:

- **Acute Procedural Success (APS)**, the electrical isolation of ≥ 3 pulmonary veins from the left atrium as reported after the first procedure (ES).
- **Chronic Treatment Failure (CTF)**, defined as Detectable AF during the Non Blanked Follow-up Period, or use of Non Study AF Drugs, or an AF Intervention through the 12 month follow-up visit. The protocol stipulated that subjects could not be counted as a CTF for Detectable AF during the 90 day blanking period. However, subjects could have a CTF for use of Non Study AF Drugs or AF Intervention during the 90 day blanking period.
- **Treatment Success (TS)**, defined as:
  - **Experimental Subjects:** Acute Procedural Success and Freedom from Chronic Treatment Failure.
  - **Control Subjects:** Freedom from Chronic Treatment Failure.

Acute Procedural Success: Acute Procedural Success was achieved in 98.2% of ES. Electrical isolation was achieved in >95% of each of the 4 main pulmonary veins attempted. Electrical isolation was assessed by pacing to determine electrical conduction between the pulmonary vein and left atrium had been interrupted, by evidence of entrance and, where assessable, exit block (Table 10).

Table 10. Experimental First Procedures: Acute Pulmonary Vein Isolation rates

Vein(s)	Proportion Isolated % (n / N)
≥ 3 PVs (APS[a])	98.2% (160 / 163)
RSPV[b]	98.1% (159 / 163)
RIPV[b]	97.4% (152 / 156)
LSPV[b]	96.7% (146 / 151)
LIPV[b]	97.4% (149 / 153)

[a] APS = Acute Procedural Success
[b] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior

Treatment Success: The Primary Effectiveness Outcome, Treatment Success, was observed in 69.9% of ES and 7.3% of CS (difference 62.6%, p < 0.001). (See Figure 1 and Table 11).

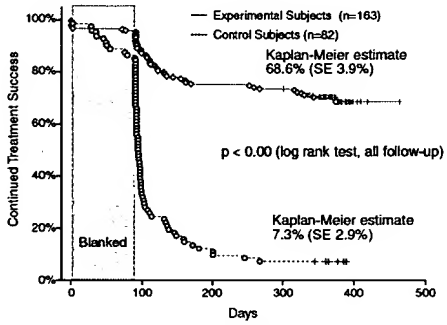


Figure 1. Kaplan Meier Display of Continued Treatment Success by Group Through 12 months, Modified Intent to Treat Population

Table 11. Primary effectiveness outcome: Treatment success (mITT Population)

Primary effectiveness outcome	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	p value
Treatment success	7.3% (6 / 82) [2.7, 15.2%]	69.9% (114 / 163) [62.3, 76.9%]	62.6% [53.6, 71.6%]	<0.001

Additional Measures of Effectiveness: Other relevant measures confirmed treatment effectiveness for PAF:

- **AF Drug Free Treatment Success:** Of the 114 ES with Treatment Success, 101 (62.0%) were Treatment Successes without the use of any AF Drugs at any time during the Non Blanked Follow-up Period.
  - 62.0% (101/163) of experimental subjects were off AF drugs during the entire non-blanked follow-up period, while 8% (13/163) of the experimental subjects that were considered treatment successes were treated with a previously failed AF drug during the non-blanked follow-up period (Table 11).

Table 12. Treatment Success and Atrial Fibrillation Drug Therapy

AF Drug Status during Non-Blanked Follow-up Period	Control Subjects % (n / N) [95% CI] N = 82	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment Success	7.3% (6 / 82) [2.7, 15.3%]	69.9% (114 / 163) [62.3, 76.9%]
Treatment Success Without Any AF Drugs[2]	0.0% (0 / 82) [0.0, 4.4%]	62.0% (101 / 163) [54.0, 69.4%]
Treatment Success With Any AF Drugs[3]	7.3% (6 / 82) [2.7, 15.3%]	8.0% (13 / 163) [4.3, 13.3%]

- **Reduced Use of AF Drugs:** 74% of all ES were off AF Drugs during the last 3 months of follow-up, and 87% of ES with Treatment Success were free from any AF Drug use during the last 3 months of follow-up.
- **Improved Quality of Life:** ES showed significantly improved SF-36 quality of life score through 12 months of follow-up in every subscale.
- **Reduced Symptoms:** ES had a significant reduction in AF symptomatic burden after cryoablation. At baseline 100% of patients had symptoms, at 12 months only 20% had symptoms from PAF.
- **Effectiveness by Balloon Size:** Treatment success was 70% among cryoablations with balloon size 23mm, 63.3% among cryoablations with balloon size 28mm, and 76.2% among subjects with both balloon sizes utilized (Table 13).

Table 13. Primary Effectiveness Outcome; Proportion of ES with Treatment Success at the 12 Month Follow-up Visit

Cohort	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment success	69.9% (114 / 163) [62.3, 76.9%]
By balloon size:	
Balloon size 23 only	70% (35 / 50) [55.4, 82.1%]
Balloon size 28 only	63.3% (31 / 49) [48.3, 76.6%]
Both balloon sizes	76.2% (48 / 63) [63.8, 86.0%]

- **Effectiveness by number of procedures performed:** A post-hoc analysis revealed that procedure sequence had an impact on treatment success in the STOP AF trial. Figure 2 illustrates that treatment success improved as the number of procedures performed increased at a given site (see Table 13 and Figure 2).

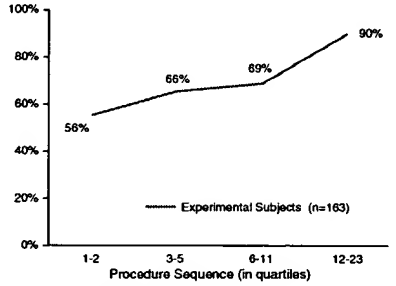


Figure 2. Procedure Frequency and Treatment Success

Atrial Flutter: Adjunctive cryoablation of the cavo-tricuspid isthmus (CTI) was performed in 66 ES. Bi-directional block was achieved in 97.0% of these subjects at the first attempt. Freedom from Flutter Chronic Treatment Failure (Flutter CTF) was observed in 70.7% (29 / 41) of those subjects with a history of atrial flutter at baseline and 84.0% (21 / 25) of those subjects with no history of atrial flutter at baseline.

5.7 Safety outcomes and measures

Serious Adverse Events were defined as any undesirable clinical occurrence in a study subject that included any of the following events:

- Any adverse event resulting in death
- Any adverse event, which is life-threatening
- Any adverse event resulting in inpatient hospitalization > 48 hours or prolongation of existing hospitalization by two or more days
- Any adverse event resulting in a persistent, significant disability or incapacity
- Any adverse event resulting in a congenital anomaly or birth defect

Primary Safety Outcome Measures were defined as:

- **Cryoablation Procedure Events** (CPEs), assessed only for ES for procedural safety, which were device or procedure-related serious adverse events (SAE) categorized as access site complications, cardiac damage, PV stenosis, embolic complications, arrhythmias, unresolved phrenic nerve palsy, and death; and
- **Major Atrial Fibrillation Events** (MAFEs), which were serious adverse events categorized as cardiovascular death, myocardial infarction, stroke, or hospitalization for AF. Overall disease and treatment morbidity, exclusive of the experimental cryoablation procedure, was assessed for both the control and experimental treatment subjects by this measure.

Primary Safety Outcomes (two were defined by the STOP AF Study Protocol):

- The proportion of experimental group safety subjects with one or more CPEs.
- The proportion of safety subjects in either group free of MAFEs at the 12 month follow-up visit.

Both safety outcomes met pre-specified criteria and success was achieved for the safety evaluation.

Cryoablation Procedure Events: Data for subjects who were randomized to the experimental therapy and received treatment are included in the analysis of CPE shown in the following table. ES had a 3.1% (6.3% UCB) rate of CPE compared to a pre-specified UCB of 14.8% ($p < 0.001$). Observed CPEs included 2 instances of cardiac damage (one peri-procedural MI, one perforation with tamponade), one arrhythmia, and two cases of pulmonary vein stenosis (Table 14).

Table 14. Primary safety outcome: Cryoablation procedure events

Primary safety outcome: CPE	Experimental subjects % (n / N)	95% upper confidence bound	p value
Experimental subjects with one or more CPE	3.1% (5 / 163)	6.3%	<0.001

Table 15 lists the individual CPEs that were reported during the STOP AF trial.

Table 15. Experimental Subjects; Cryoablation Procedure Event Categories

CPE Categories	Experimental Subjects % (n) N = 163	95% One-Sided Upper Confidence Bound[a]
Access site complications	0.0% (0)	1.8%
Cardiac damage (including myocardial infarction)	1.2% (2)	3.8%
Embolic phenomena (including stroke)	0.0% (0)	1.8%
Arrhythmias	0.6% (1)	2.9%
Persistent phrenic nerve injury[b]	0.0% (0)	1.8%
Death	0.0% (0)	1.8%
Pulmonary vein stenosis[c]	1.2% (2)	3.8%

[a] Based on Clopper-Pearson confidence intervals

[b] Four (4) Experimental subjects had phrenic nerve injury persisting at 12-months of follow-up; none were adjudicated as SAE. They were not included as a CPE because they were not adjudicated as an SAE.

[c] Five (5) Experimental Subjects had one or more pulmonary veins with stenosis during study follow-up; 2 of these adverse events were adjudicated as SAE.

Pulmonary Vein Stenosis: The PV stenosis rate was 3.1% (5/163) in ES and 3.1% (7/228) for all subjects having undergone cryoablation (Table 16). Stenosis was defined in the protocol as a reduction in the calculated pulmonary vein cross sectional area to <25% of the

baseline pulmonary vein cross sectional area. Five (5) subjects had radiologic findings only, without symptoms of any kind. Two (2) subjects experienced significant symptoms and disability (i.e. Serious Adverse Event) and therefore these two pulmonary vein stenosis events were adjudicated as a CPE.

Table 16. Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects

Proportion of Subjects	Experimental			Control	All Subjects
	One Cryoablation[a] % (n) [95% CI][b] N = 132	Two Cryoablations (n) [95% CI][b] N = 31	Any Cryoablation % (n) [95% CI][b] N = 163	One Cryoablation (n) [95% CI][b] N = 65	Any Cryoablation (n) [95% CI][b] N = 228
Stenosis in ≥1 PV at 6 or 12 Months[c]	2.3% (3) [0.5, 6.5%]	6.5% (2) [0.8, 21.4%]	3.1% (5) [1.0, 7.0%]	3.1% (2) [0.4, 10.7%]	3.1% (7) [1.2, 6.2%]

[a] One ES also had RF ablation for atrial fibrillation 72 days after the initial cryoablation.
[b] Clopper-Person confidence intervals.
[c] Each subject is counted only once within each time point.
CI = confidence interval, PV = pulmonary vein.

Phrenic Nerve Palsy: Twenty-nine (29) occurrences of Phrenic Nerve Palsy (PNP) in 28 subjects were reported (Table 17). Overall, 11.2% (29 / 259) of all cryoablation procedures were associated with PNP. Twenty-five (25) (11%) were associated with PNP, which resolved within 12 months of follow-up, and 4 (1.8%) were associated with persistent PNP (Table 18). Fifteen (15) subjects were asymptomatic, 13 had one or more associated symptoms including dyspnea on exertion (6), dyspnea (5), shortness of breath (2), orthopnea (2) and cough (1) during the period in which hemi-diaphragmatic abnormalities were noted. One occurrence of PNP was adjudicated as an SAE.

Table 17. Phrenic Nerve Palsy; Procedures

Phrenic Nerve Palsy	First Experimental Ablation Subjects % (n) [95% CI] N = 163[a]	Experimental Reablation Subjects % (n) [95% CI] N = 31[a]	Crossover Control Ablation Subjects % (n) [95% CI] N = 65[a]	All Ablated Subjects % (n) [95% CI] N = 228[a]
Procedures free of PNP[b]	87.7% (143) [81.7, 92.3%]	90.3% (28) [74.2, 98.0%]	90.8% (59) [81.0, 96.5%]	88.8% (230) [84.3, 92.4%]
Procedures associated with PNP[b]	12.3% (20) [7.7, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.2% (29) [7.6, 15.7%]

[a] N = the total number of subjects undergoing cryoablation procedures of this type.
[b] One subject had 2 events of PNP, one with the first experimental cryoablation and one with the second, reablation procedure (both of which resolved).

Table 18. Phrenic Nerve Palsy; Subjects

Phrenic Nerve Palsy	First Experimental Ablation Procedures % (n) [95% CI] N = 163[a]	Experimental Reablation Procedures % (n) [95% CI] N = 31[a]	Crossover Control Ablation Procedures % (n) [95% CI] N = 65[a]	All Ablation Procedures % (n) [95% CI] N = 259[a]
All Subjects with PNP	12.3% (20) [7.6, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	12.3% (28) [8.3, 17.3%]
Persistent PNP (radiographic)	2.5% (4) [0.7, 6.2%]	0.0% (0) [0.0, 11.2%]	0.0% (0) [0.0, 5.5%]	1.8% (4) [0.5, 4.4%]
Resolved PNP (radiographic)	9.8% (16) [5.7, 15.5%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.0% (25) [7.2, 15.8%]

[a] N = the total number of cryoablation procedures of this type.

Major Atrial Fibrillation Events: Data for subjects who were randomized to either experimental or drug treatment, received such treatment and were followed through 12 months post treatment start are included in the analysis for MAFE shown in the following table. The analysis was an evaluation of non-inferiority of MAFE rates in ES compared to Control. The clinically significant difference (δ) for establishing noninferiority for the MAFE free rate was set at 10% ES had a 96.9% Freedom from MAFE rate, compared to CS who had a 91.5% rate ($p < 0.0001$, non-inferiority for difference ≤ 10%) (see Table 19).

Table 19. Primary safety outcome: Freedom from MAFE

Primary safety outcome: Freedom from MAFE	Control subjects % (n /N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	Test for non-inferiority $\delta = 0.10$ p value
Freedom from MAFE (through 12 month follow-up)	91.5% (75 / 82) [83.2, 96.5%]	96.9% (158 / 163) [93.0, 99.0%]	5.4% [-1.1, 12.1%]	<0.001

The observed categories of MAFEs are displayed for both treatment groups below (Table 20).

Table 20. Subjects with one or more MAFEs by category, safety population

MAFE Categories	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% 95% CI]	Difference [95% CI]	p value
Any MAFE	8.5% (7 / 82) [3.5, 16.8%]	3.1% (5 / 163) [1.0, 7.0%]	-5.4% [-12.1, 1.1%]	0.112
Cardiovascular death	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Hospitalization for:	7.3% (6 / 82) [2.7, 15.2%]	1.8% (3 / 163) [0.4, 5.3%]	-6.5% [11.5, 0.5%]	0.064
AF recurrence or ablation	6.1% (5 / 82) [2.0, 13.7%]	0.6% (1 / 163) [0.0, 3.4%]	-5.5% [-10.8, -0.2%]	0.017
Atrial flutter ablation (excluding Type I)	1.2% (1 / 82) [0.0, 6.6%]	0.0% (0 / 163) [0.0, 2.2%]	-1.2% [-3.6, 1.2%]	0.335
Systemic embolization (not stroke)	0.0% (0 / 82) [0.0, 4.4%]	0.0% (0 / 163) [0.0, 2.2%]	NA	NA
Congestive heart failure	0.0% (0 / 82) [0.0, 4.4%]	1.2% (2 / 163) [0.1, 3.4%]	-1.2% [-5.0, 2.5%]	1.000
Hemorrhagic event (not stroke)	2.4% (2 / 82) [0.3, 8.5%]	1.2% (2 / 163) [0.1, 4.4%]	-1.2% [-5.0, 2.5%]	0.603
Anti-arrhythmic drug: initiation, adjustment, or complication[a]	4.9% (4 / 82) [1.3, 12.0%]	0.6% (1 / 163) [0.0, 3.4%]	-4.3% [-9.1, 0.5%]	0.044
Myocardial infarction	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Stroke	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000

[a] Excludes control subject treatment initiation

As described in Table 21, only 1 ES had a MAFE categorized as stroke. There was an additional 4 (3 ES and 1 CS) strokes reported during the 12 month follow-up. All 4 subjects had recovered completely at the time of the 12 month follow-up. Table 21 provides additional detail for the 5 strokes that were reported during the 12 month follow-up (1 MAFE stroke, 4 non-MAFE stroke).

Table 21. Subjects with Stroke During Study Follow-up

Group	Diagnosis (verbatim)	Onset	Ablation Related[a]	Clinical Outcome	Event Severity	SAE
Exp	Small hemorrhagic stroke	Day 183	No	Recovered completely	Mild	No
Exp	Lacunar infarct	Day 51	Unknown[b]	Recovered completely	Mild	No
Cont	Stroke	Same day as X-over ablation	Yes	Recovered completely	Severe	No
Exp	"Sees white spots in both eyes"	~1 month after cryoablation	No	Recovered completely	Mild	No
Exp	Subarachnoid hemorrhage	Day 260	No	Recovered completely	Severe	Yes

[a] Ablation-related = procedure-related or device-related adverse event.
[b] Age of infarct indeterminate when discovered and could not be temporally linked to procedure or device. Adjudicated as of unknown relatedness
Exp = Experimental, Cont = Control, X-over = crossover

5.8 Additional safety information from the STOP AF Pivotal Trial

5.8.1 Serious adverse events (SAE)

A total of 55 serious adverse events (SAE) in 32 study subjects were reported by investigators during the first 12 months of study follow-up (See Table 22). Twenty-two (22) SAE occurred in 12 CS (12 MAFE and 10 other SAE) (See Table 23) and 33 SAE occurred in 20 ES (5 CPE, 8 MAFE and 20 other SAE) (See Table 22). The overall proportion of CS with one or more SAE was 14.6% and for ES was 12.3%, a slightly lower rate of SAE occurrence that was not significantly different (p = 0.688).

Table 22. Subjects with one or more serious adverse events, safety population

Serious adverse events	Control subjects % (n /N)	Experimental subjects % (n / N)	Difference [95% CI]	p value
Serious adverse events	14.6% (12 / 82)	12.3% (20 / 163)	-2.3% [-11.5, 6.8%]	0.688

The SAE occurring in CS and ES are listed in the following tables (Table 23 and Table 22).

Table 23. Serious adverse events occurring in control subjects, safety population

Serious Adverse Events	Control Subjects % (n / n) N=82
Atrial Fibrillation	4.9% (4/82)
Atrial Flutter	2.4% (2/82)
Appendicitis	1.2% (1/82)
Atrial Thrombosis	1.2% (1/82)
Cardiac Tamponade	1.2% (1/82)
Cardio Respiratory Arrest	1.2% (1/82)
Gastrointestinal Hemorrhage	1.2% (1/82)
Injection Site Infection	1.2% (1/82)
Meningitis	1.2% (1/82)
Mental Status Changes	1.2% (1/82)
Pericardial Effusion	1.2% (1/82)
Phrenic Nerve Paralysis	1.2% (1/82)
Renal Failure Acute	1.2% (1/82)
Subdural Hematoma	1.2% (1/82)

Table 24. Serious adverse events occurring in experimental subjects, safety population

Serious Adverse Events	Experimental Subjects % (n / n) N=163
Pneumonia	2.5% (4/163)
Atrial Fibrillation	1.2% (2/163)
Deep Vein Thrombosis	1.2% (2/163)
Myocardial Infarction	1.2% (2/163)
Pulmonary Vein Stenosis	1.2% (2/163)
Asthenia	0.6% (1/163)
Asthma	0.6% (1/163)
Atrial Flutter	0.6% (1/163)
Cardiac Tamponade	0.6% (1/163)
Cardiopulmonary Failure	0.6% (1/163)
Escherichia Bacteremia	0.6% (1/163)
Gastrointestinal Hemorrhage	0.6% (1/163)
Ileitis	0.6% (1/163)
Multi Organ Failure	0.6% (1/163)
Pneumonitis	0.6% (1/163)
Pneumothorax	0.6% (1/163)
Pulmonary Embolism	0.6% (1/163)
Pyelonephritis Acute	0.6% (1/163)
Sepsis	0.6% (1/163)
Soft Tissue Hemorrhage	0.6% (1/163)
Subarachnoid Hemorrhage	0.6% (1/163)
Vessel Puncture Site Hematoma	0.6% (1/163)
Wegener S Granulomatosis	0.6% (1/163)

5.8.2 Death summary

No study subject died within 30 days of a cryoablation procedure. There was one death during the 12 month follow-up period. A 68 year old male Experimental Subject died shortly after a witnessed cardiac arrest occurring 10 months after cryoablation. The event was determined to be unrelated to the study devices, ablation procedure or approved anti-arrhythmic drug therapy.

5.8.3 Pulmonary vein stenosis

PV stenosis was defined by the study protocol as a 75% reduction in area which is roughly a 50% decrease in diameter. Assessment for PV dimensions was done at baseline of 6 and 12 months via CT/MRI scans. Seven of 228 (3.1%) cryoablated study subjects (5 ES and 2 Crossover CS) had one or more stenosed pulmonary veins (PVs) detected during study imaging. Two subjects were symptomatic and their pulmonary vein stenosis adverse events were adjudicated as SAEs and CPEs. Intervention was recommended for both subjects; one declined and the other had angioplasty and stenting with symptomatic improvement. Based on a multivariate analysis there are no known contributing factors to the incidence of PV stenosis.

5.8.4 Phrenic nerve injury

Cryoablation was associated with a high incidence of Transient Phrenic Nerve Dysfunction (TPND) occurring during procedures, which resolved by the end of the procedure and were almost always unassociated with subsequent phrenic nerve dysfunction. Phrenic nerve palsy (PNP), new onset hemi-diaphragmatic movement disorder detected by radiologic assessment, was found after 11.2% (29 / 259) of all cryoablation procedures of which 15 (51.7%) were asymptomatic. All but 4 cases resolved by the end of study follow-up, taking a mean of 158.2 days (range 1 to 407). Three of 4 persistent PNP cases were symptomatic during follow-up, but none were disabling and only 1 persistent PNP subject had symptoms at the 12 Month visit. Based on a multivariate analysis there are no known contributing factors to the incidence of Phrenic Nerve Palsy.

5.8.5 Strokes and TIAs

Strokes occurred in 5 study subjects (4 ES and 1 CS); only one of these was related to a cryoablation procedure or the devices in a Crossover Control Subject. Of these 5 strokes, one was a subarachnoid hemorrhage from an anterior cerebral artery aneurysm, another was characterized as "whites spots in both eyes" and stroke could not be excluded, and one was a small lacunar stroke found incidentally during a work-up of dizziness. All 5 strokes recovered completely by the conclusion of study follow-up.

5.8.6 Esophageal injury

Esophageal ulcerations have been observed in some subjects who undergo cryoablation with the Arctic Front Cryoablation Catheter. As with other forms of left atrial ablation, the physician should consider appropriate medical strategies to minimize the risk of esophageal injury.

One (1) investigational center performed esophagogastroduodenoscopy post-cryoablation procedure on 12 STOP AF subjects. Of the 12 subjects, 3 were discovered to have esophageal ulcerations. All 3 subjects had follow-up esophagogastroduodenoscopy and demonstrated resolution of esophageal ulceration.

5.8.7 Vascular access complications

Other than routine cases of bruise, hematoma and discharge, there were 4 procedures (4 / 259, 1.5%) associated with significant vascular access site adverse events requiring surgical intervention or transfusion: 1 new AV fistula, 1 worsened pre-existing AV fistula, 2 pseudoaneurysms, and one hemorrhage requiring transfusion. One subject had both an AV fistula and a pseudoaneurysm.

5.9 Summary of STOP AF Pivotal Trial adverse events as categorized using MedDRA

There were a total of 1,406 adverse events (AEs) reported in 235 study subjects during the 12 month period of study follow-up. Seventy-six (76) CS experienced 485 AEs and 159 ES experienced 921 AEs. Ten (10) study subjects had no AEs reported, 6-CS and 4-ES.

In total, 69.2% (45/65) of Crossover CS and 75.5% (123/163) of ES experienced at least one **procedure-related AE**. Overall, the most frequently reported procedure-related AEs (higher than 10%) were back pain (35 subjects, 15.4%) and vessel puncture site hematoma (26 subjects, 11.4%). Other fairly common (higher than 5%) procedure-related AEs included pharyngolaryngeal pain (22 subjects,9.6%), cough (21 subjects, 9.2%), nausea (19 subjects, 8.3%), and procedural pain (15 subjects, 6.6%).

A greater proportion of ES (46.0%) experienced at least one device-related AE compared to Crossover CS (23.1%). The most frequently reported device-related AEs (higher than 10%) were in the following System Organ Class (SOC): Injury, Poisoning and Procedural Complications (Control:12.3%; Experimental: 18.4%), Nervous System Disorders (Control:13.8%; Experimental: 16.6%), Respiratory, Thoracic and Mediastinal Disorders (Control: 6.2%; Experimental: 12.3%), and General Disorders and Administration Site conditions (Control: 4.6%; Experimental: 11.0%). Overall, the only device-related AE occurring in greater than 10% of all cryoablated subjects was phrenic nerve paralysis (28subjects, 12.3%). Other common (higher than 5%) device-related AEs included nerve injury (22 subjects, 9.6%), cough (15 subjects, 6.6%) and venous injury (14 subjects, 6.1%). The majority of the device-related AEs that were observed occurred in less than 2% of subjects.

5.10 Study conclusion

The STOP AF Pivotal Trial demonstrated that there is a reasonable assurance of safety and effectiveness to support the use of the Arctic Front Cardiac CryoAblation Catheter, the Freezor MAX Cryocatheter, FlexCath Steerable Sheath and the CryoConsole (Gen V) in the treatment of patients with drug resistant paroxysmal atrial fibrillation.

6 Adverse events

Potential adverse events associated with cardiac catheter cryoablation procedures include, but are not limited to, the following conditions:

- Anemia
- Anxiety
- Atrial flutter
- Back pain
- Bleeding from puncture sites
- Blurred vision
- Bradycardia
- Bronchitis
- Bruising
- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Cough
- Death
- Diarrhea
- Dizziness
- Esophageal damage
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Nerve injury
- Pericardial effusion
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Tachycardia
- Transient ischemic attack
- Urinary infection
- Vasovagal reaction
- Visual changes

7 Instructions for use

7.1 Connecting the catheter

To connect the catheter, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual.*)

1. Connect the non-sterile auto connection box to the CryoConsole.
2. Connect the Arctic Front cryoballoon to a sterile coaxial umbilical cable and a sterile electrical umbilical cable in a dry environment.
3. Connect the coaxial umbilical cable to the CryoConsole and connect the electrical umbilical cable to the auto connection box.

Note: The ECG cable is not required for an Arctic Front procedure, and should not be connected to the non-sterile auto connection box.

Note: If the balloon cannot be inflated or deflated using the CryoConsole, have a Manual Retraction Kit on hand during the procedure.

7.2 CryoAblation

To use the catheter for a cryoablation procedure, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual*.)

Note: Prior to introducing the Arctic Front into the patient, test the deflection mechanism by pulling on the lever on the handle to ensure it is operational.

Note: Always use the lever on the handle to straighten the distal segment before insertion or withdrawal of the catheter.

1. Using an aseptic technique, create a vascular access with an appropriate introducer. Obtain left atrial, transseptal access using a transseptal sheath and needle.
   - Place standard diagnostic pacing catheters.
   - Visualize left atrial anatomy to help select a balloon size, select balloon size.
   - Selection of balloon size should be based on PV diameter and shape, the surrounding anatomy, and desired position of the balloon outside the tubular portion of the PV. PV diameter ranges are recommended as follows:
     a) 23 mm balloon: 10-21 mm
     b) 28 mm balloon: 16-30 mm
2. Soak the balloon and sleeve then pull back the sleeve making sure the sleeve is still submerged.
3. Exchange the transseptal sheath over the guide wire for the FlexCath Sheath.
4. Insert the Arctic Front Cryocatheter over the guide wire into the FlexCath Sheath.
5. Under fluoroscopic guidance, track a 0.032" to 0.035" guide wire to the target pulmonary vein. Advance the Arctic Front cyrocatheter over the guide wire into the left atrium.
6. Set the treatment time on the CryoConsole screen, the preset ablation duration is 240 seconds.
7. Inflate the balloon in the left atrium.
8. To occlude blood flow, position the catheter at the ostium of the target pulmonary and not inside the tubular portion of the PV.
9. Verify the balloon position for complete occlusion.
   Note: If using a mixture of 50/50 contrast/saline be sure to flush the guide wire lumen with saline after each contrast injection.
10. Perform the cryoablation.
11. Wait for the cryoablation phase to complete (at the end of the preset time). The balloon remains inflated and the Thawing phase begins.
12. During the Thawing phase, watch the temperature indicator on the screen. When it reaches 10 °C, advance the blue push button on the catheter handle. Maintain pressure on the push button until the balloon deflates. The balloon deflates automatically when the temperature reaches 20 °C.
    Note: Advancing the push button on the catheter handle during balloon deflation stretches the balloon to maximum length allowing the folds in the balloon material to wrap tightly, reducing the profile of the balloon segment for ease of re-entry into the sheath.
13. As needed, perform additional treatments by positioning the balloon differently in the same pulmonary vein.
14. Position the catheter at the ostium of the next target pulmonary vein using the guide wire and/or deflection capabilities. Return to Step 7 and continue ablation.
15. Determine effective ablation of the cardiac tissue by assessing electrical isolation of the pulmonary vein from the left atrium after the cryoablation treatments have been completed.
16. After all treatments are completed, and after the balloon is deflated retract the catheter into the sheath.
17. Remove the catheter from the patient.

8 Specifications

Catheter shaft size	3.5 mm (10.5 Fr)
Tip outer diameter	3 mm (9 Fr)
Recommended introducer sheath	12 Fr FlexCath Steerable Sheath
Inner diameter of guide wire lumen	1.3 mm (0.049 in)
Inflated balloon diameter	Model 2AF232 - 23 mm Model 2AF282 - 28 mm
Shaft length (inflated)	100 cm
Number of thermocouples	1
Environmental parameters	
Storage	Greater than 0 °C (32 °F)
Operation	15 °C to 30 °C (60 °F to 86 °F) at altitudes less than 2400 meters (8000 feet) above sea level

9 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

10 Service

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. Medtronic also maintains a professional staff to provide technical consultation to product users. For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate telephone number or address listed on the back cover.

World Headquarters
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432-5604
USA
www.medtronic.com
Tel. +1-763-514-4000
Fax +1-763-514-4879

Manufacturer
Medtronic CryoCath LP
16771 Chemin Ste-Marie
Kirkland, QC H9H 5H3
Canada
www.medtronic.com
Tel. +1-514-694-1212
Fax +1-514-694-6279
Technical Support +1-877-464-2796

Medtronic E.C. Authorized Representative/Distributed by
Medtronic B.V.
Earl Bakkenstraat 10
6422 PJ Heerlen
The Netherlands
Tel. +31-45-566-8000
Fax +31-45-566-8668

Europe/Africa/Middle East Headquarters
Medtronic International Trading Sàrl
Route du Molliau 31
Case Postale 84
CH-1131 Tolochenaz
Switzerland
www.medtronic.com
Tel. +41-21-802-7000
Fax +41-21-802-7900

Technical manuals:
www.medtronic.com/manuals

30016-027 Rev-00/M941416A001B
2010-12-15

4.0 DEVICE DESCRIPTION

4.1 Overview

The Arctic Front® Cardiac CryoAblation Catheter and CryoConsole [Arctic Front® Cryocatheter System] are indicated for the treatment of drug refractory paroxysmal atrial fibrillation. The Freezor® *MAX* Cardiac CryoAblation Catheter [Freezor® *MAX* Cryocatheter] can be used as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with Arctic Front® Cryocatheter.

The Arctic Front® Cryocatheter is a flexible, single-use, minimally invasive cryoablation catheter designed to create transmural lesions around the ostia of the pulmonary veins to treat cardiac arrhythmias. The Freezor® *MAX* Cryocatheter is a flexible, single-use, minimally invasive cryoablation catheter designed to create focal lesions to treat cardiac arrhythmias. Both catheters are compatible with the same CryoConsole and are used with several accessories (described in the following sections) to produce controlled cryogenic (extremely cold) temperatures to treat arrhythmias in a minimally invasive, precise, percutaneous manner. The procedure is performed to correct electrophysiological abnormalities leading to irregular or errant heartbeats. The device selectively destroys (ablates) groups of heart cells (arrhythmogenic sites), which cause or propagate the abnormality.

The devices listed in the table below with the specified trade names, catalog numbers, and primary distinguishing features are the subject of the PMA application.

Device Trade Names	**Catalog Numbers**	**Features**
Arctic Front® Cardiac CryoAblation Catheter	2AF232	23 mm balloon diameter
	2AF282	28 mm balloon diameter
Freezor® *MAX* Cardiac CryoAblation Catheter	239F3 (medium)	Blue curve (55mm reach)
	239F5 (long)	Orange curve (66 mm reach)
CryoConsole	106A2	
Manual Retraction Kit	20MRK	

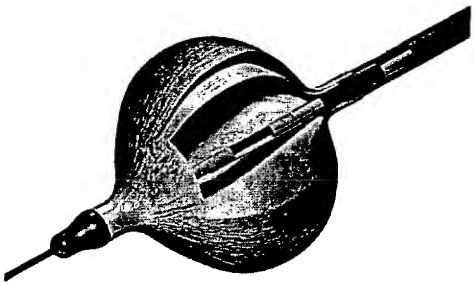
For ease of reference throughout the submission, the "short" device names listed in the table below are used. Please note that the FlexCath® Steerable Sheath, while discussed in this PMA, has already been cleared for marketing under K081049.

Device Trade Names	Device Short Names
Arctic Front® Cardiac CryoAblation Catheter	Arctic Front® Cryocatheter
CryoConsole	CryoConsole
Arctic Front® Cardiac CryoAblation Catheter and CryoConsole	Arctic Front® Cryocatheter System
Freezor® *MAX* Cardiac CryoAblation Catheter	Freezor® *MAX* Cryocatheter
Manual Retraction Kit	Manual Retraction Kit
FlexCath® Steerable Sheath	FlexCath® Sheath

4.2 Arctic Front® Cardiac CryoAblation Catheter

The Arctic Front® Cardiac CryoAblation Catheter [Arctic Front® Cryocatheter] is a sterile, single-use deflectable, over-the-wire, balloon catheter designed to create circumferential, transmural lesions at the antrum of the pulmonary veins via a transseptal approach to the left atrium (Figure 1). The Model 2AF232 has a 23 mm balloon and the Model 2AF282 has a 28 mm balloon.

Figure 1 Arctic Front® Cryocatheter



The Arctic Front® Cryocatheter is used together with the FlexCath Sheath, as well as the CryoConsole and related components. The catheter is introduced into the vasculature and positioned in the heart by traditional minimally invasive techniques. Liquid refrigerant is injected into the balloon from the CryoConsole. As the liquid evaporates, it absorbs heat from the tissue contacting the balloon, freezing the tissue. The warmed vapor returns to the CryoConsole through a vacuum lumen within the shaft of the catheter and the coaxial umbilical cable. A thermocouple positioned inside the balloon provides temperature reading capability.

4.3 Freezor® *MAX* Cardiac CryoAblation Catheter

The Freezor® *MAX* Cardiac CryoAblation Catheter [Freezor® *MAX* Cryocatheter] is a flexible, steerable catheter used to ablate cardiac tissue (Figure 2). The Model 239F3 (medium) has a blue curve with a 55mm reach and the Model 239F5 (long) has an orange curve with a 66 mm reach.

Figure 2 Freezor® MAX Cryocatheter

The Freezor® *MAX* Cryocatheter is used together with the CryoConsole and related components. The catheter is introduced into the vasculature by traditional minimally invasive techniques. The tip of the Freezor *MAX* Cryocatheter reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the tip of the catheter, freezing the adjacent tissue. The catheter tip has an integrated thermocouple for temperature reading capability.

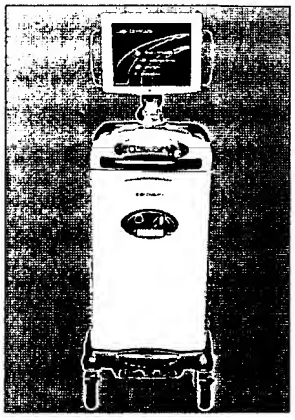
The Freezor® *MAX* Cryocatheter was used in the clinical studies as an adjunctive device to the Arctic Front® Cryocatheter for gap cryoablation to complete electrical isolation of the pulmonary veins, cryoablation of focal trigger sites, and creation of atrial flutter line between the inferior vena cava and the tricuspid valve.

The Freezor® *MAX* Cryocatheter is already approved under P020045/S007 as a surgical device for minimally invasive cardiac surgery procedures, including surgical treatment of cardiac arrhythmias. The PMA-approved Freezor® *MAX* device is named the Freezor® MAX Surgical Cryoablation device and is identical to the Freezor® *MAX* Cryocatheter except that the surgical device includes a white, 12" thermal insulation sheath on the shaft near the strain relief at the proximal end.

4.4 CryoConsole

The CryoConsole Model 106A2 produces controlled cryogenic (extreme cold) temperatures at the tip of a long, flexible focal or balloon catheter, which can be inserted into the patient. The purpose of the system is to deliver cold energy to the left atrium by approaching the heart through the body's vasculature from punctures in the skin. The CryoConsole is an electro-mechanical system with a touch screen software user interface (Figure 3, v001:p055).

Figure 3 CryoConsole



The CryoConsole is for use in performing cardiac ablation procedures. During a procedure, pressurized liquid N_2O (nitrous oxide) refrigerant is injected from a tank in the CryoConsole. The refrigerant travels through an ultra-fine injection tube which passes through the coaxial umbilical cable and the catheter shaft to the tip of the cryoablation catheter. The collected vapor is evacuated by the CryoConsole into the hospital suction or evacuation system. The CryoConsole provides comprehensive procedural information and control, as well as multiple hardware and software safety features.

At power-up, the console performs a series of self-tests and verifications ensuring functions and safety systems are functional. The series of tests are: software integrity, interface software/hardware, functionalities and all the safety features. Once the console has completed the self-verification process a main panel is displayed on the touch screen showing four options: Begin CryoTherapy, Review Patient Records, Service System, Shut down system.

The safety of the operation is monitored by the system during all phases of the procedure for events such as catheter breach, abnormal level of vacuum, improper catheter connections, abnormal refrigerant flow and loss of electrical connection. Abnormalities related to these events result in automatic discontinuation of the injection of refrigerant and display of a system notice indicating the nature of the problem and the action to take to continue.

The CryoConsole can operate with balloon (Arctic Front®) and focal (Freezor® *MAX*) cryocatheters. For focal catheters the only operating mode is ablation; however, for balloon catheter three operating modes are available (inflation, ablation and thawing).

The system relies on a highly endothermic phase transformation of the refrigerant when going from a liquid to a vapor state to generate the cryogenic temperatures at the cooling segment of the catheter. That is why the catheter's shaft under normal operation has no potential for heat transfer or inadvertent freezing as all of the energy transfer happens in the cooling segment where the refrigerant changes phase.

The umbilicals (described below) provide mechanical and electrical connections between the CryoConsole and cryocatheter for refrigerant injection and recovery, temperature reading, leak detection, blood detection and smart chip features of the catheter. A connection box is used to link standard intracardiac recording devices or pacing generators and also for electrical noise reduction. The length of the umbilical allows for flexible placement of the console with respect to the patient.

4.5 Accessories

Six accessory devices are available for use with the Arctic Front® and Freezor® *MAX* Cryocatheters and the CryoConsole to accomplish a cryoablation procedure: Coaxial Umbilical, Electrical Umbilical, Auto-Connection Box, ECG Cable, Footswitch, and Manual Retraction Kit. All devices, except the Manual Retraction Kit, are already PMA-approved.

Coaxial Umbilical

The coaxial umbilical is used to deliver the liquid refrigerant from the console to the catheter and to transport refrigerant vapors from the catheter to the console, which are then vented into the hospital scavenging system. This umbilical accessory, which is provided sterile, is already approved as part of the Freezor® Cardiac CryoAblation System (P020045).

Electrical Umbilical

The electrical umbilical, which connects the catheter to the auto connection box, is a 16-wire cable with a 25-pin male connector at one end and a 25-pin female connector at the other end. The purposes of this umbilical are to:

- transport temperature feedback and the leak detection signal from the catheter to the console via the connection box
- transport the pressure sensor signal from the catheter to the console via the connection box
- transport the blood detection board signal from the catheter to the console via the connection box

This umbilical accessory, which is provided sterile, is already approved as part of the Freezor® Cardiac CryoAblation System (P020045).

Auto-Connection Box

The Auto-Connection Box provides a noise-free intracardiac electrogram (only applicable to the Freezor® MAX Cryocatheter). With the Arctic Front® Cryocatheter, the Auto Connection Box is used simply as an extension to the electrical umbilical. The Auto-Connection Box, which is provided non-sterile, is already approved as part of the Freezor® Cardiac CryoAblation System (P020045)

ECG Cable

The ECG cable is used to connect the Auto Connection Box to the hospital's electrophysiology system. The ECG cable is 34 inches in length and splits into 4 ECG cables labeled with "D", "2", "3," and "4". The ECG Cable is provided non-sterile. ECG signals are sensed by three (3) ECG rings and the tip electrode of the focal catheter (Freezor® *MAX*

Cryocatheter). The three (3) ECG rings and the tip electrode transport the ECG signal respectively through three (3) ECG wires and a thermocouple. All travel through the length of the lumen of the catheter and are connected to the electrical cable of the catheter. The ECG Cable accessory is already approved as part of the Freezor® Cardiac CryoAblation System (P020045).

Footswitch

The footswitch is a foot-activated remote control device whose function is to enable and stop the injection of refrigerant. The purpose of this accessory is to enable holding the catheter for positioning at the same time as enabling/disabling the injection with the footswitch. The footswitch connects to the back of the CryoConsole and is provided non-sterile. The footswitch accessory is already approved as part of the Freezor® Cardiac CryoAblation System (P020045).

This accessory is optional and was not used in the clinical studies [STOP AF Pivotal Trial (PS-023) and CAP AF Continued Access Protocol (PS-024)]. However, the footswitch will be part of the commercial Arctic Front® Cryocatheter System as an accessory device.

Manual Retraction Kit

The Manual Retraction Kit is an optional accessory that is used during the rewrap procedure of the Arctic Front® Cryocatheter if the physician cannot retract the catheter using the normal catheter retraction procedures, i.e., using the push button located at the catheter's handle. The kit contains one large syringe, one 3-way stopcock and one coaxial-to-luer adaptor. The kit is provided sterile.

4.6 Indications for Use

The Arctic Front® Cardiac CryoAblation Catheter and CryoConsole are indicated for the treatment of drug refractory paroxysmal atrial fibrillation.

The Freezor® *MAX* Cardiac CryoAblation Catheter is used as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with Arctic Front® Cryocatheter for the following uses:

- gap cryoablation to complete electrical isolation of the pulmonary veins,
- cryoablation of focal trigger sites, and
- creation of atrial flutter line between the inferior vena cava and the tricuspid valve.

4.7 Properties of Device Relevant to Indications for Use

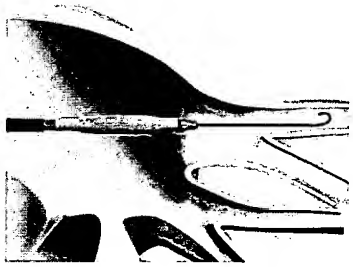
The Arctic Front® Cryocatheter is a flexible, single-use, minimally invasive cryoablation catheter designed to create transmural lesions around the pulmonary vein ostia in the left atrium to treat arrhythmias. The Freezor® *MAX* Cryocatheter is a flexible, single-use, minimally invasive cryoablation catheter designed to create focal lesions to treat arrhythmias. Used in conjunction with the CryoConsole, accessories, and the FlexCath® steerable sheath, the Arctic Front® or Freezor® *MAX* Cryocatheter is designed to create lesions in the antrum or at the ostium of the targeted pulmonary vein for the treatment of paroxysmal atrial fibrillation. The cryocatheter is inserted over a guide wire through the FlexCath® steerable sheath to the left atrium, where it can be advanced to the target vein. The CryoConsole controls the delivery of liquid nitrous oxide (N_2O) refrigerant to the cryocatheter and the return of the warmed vapor. Multiple safety features are built into the cryocatheter and console to mitigate potential hazards.

4.8 Principles of Operation

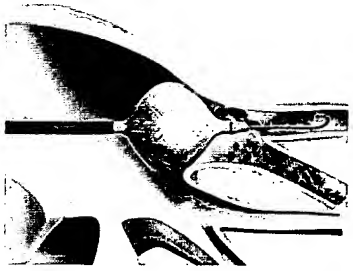
A cryoablation procedure is done to correct electrophysiological abnormalities leading to irregular or errant heartbeats. It selectively destroys (ablates) the electrical characteristics of groups of heart cells (arrhythmogenic sites), which cause or propagate the abnormality. During a procedure, pressurized liquid N_2O refrigerant is injected from a tank in the CryoConsole. The refrigerant travels through an ultra-fine tube which passes through the coaxial umbilical and the catheter shaft to the cooling segment of the catheter. The specific steps in the procedure are described in Figure 4 below.

Figure 4 Arctic Front® Cryocatheter System: Principles of Operation

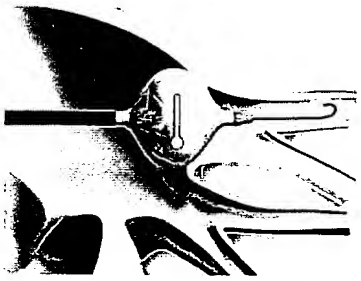
Once the FlexCath Steerable Sheath has been introduced into the left atrium via a transseptal puncture, the Arctic Front Cryocatheter is passed through the FlexCath lumen over a guidewire and into the left atrium in an uninflated state. Typically the guidewire has already been placed in the target pulmonary vein.



The Arctic Front Cryocatheter is inflated in the atrium and gently positioned at the ostium of the target pulmonary vein. Balloon position and the extent of venous occlusion are verified by injection of contrast or the use of intracardiac ultrasound.



When occlusion has been achieved, cryoablation is initiated. Refrigerant is automatically injected into the inflated balloon, removing heat and causing the balloon temperature to drop to cryoablation levels. The tissue freezes at the point of contact with the balloon, resulting in cell death and conduction block.



After the cryoablation cycle is complete, the flow of refrigerant is stopped and the Arctic Front Cryocatheter balloon warms to body temperature. The balloon is then deflated and withdrawn into the left atrium, where the procedure can be repeated in the same or another pulmonary vein.

If subsequent testing reveals gaps in the ablation line, additional balloon cryoablations can be performed, or the Freezor *MAX* Cardiac CryoAblation Catheter can be used for focal touch-ups. The Freezor *MAX* Cryocatheter can also be used to ablate other arrhythmogenic foci as needed.

4.8.1 Arctic Front® Cryocatheter Operating Modes

The Arctic Front® Cryocatheter procedure is as follows: catheter insertion, inflation and positioning, ablation and thawing.

Catheter insertion: The balloon is delivered into the left atrium in a deflated state via a 12F sheath.

Inflation and positioning: Once the targeted vein is wired, the treatment is initiated and a fixed volume of refrigerant is released and contained in the catheter in order to inflate the balloon. The balloon is advanced to occlude the vein ostium. The level of occlusion is confirmed by injecting contrast and verifying under fluoroscopy that the contrast stays in the vein (sign of a good occlusion and, therefore, good contact between the balloon and the ostium).

Ablation: The ablation is initiated by pressing the ablation button on the console's touch screen. The system begins refrigerant flow while gradually increasing refrigerant gas withdrawal. The flow of refrigerant in and out of the catheter is carefully balanced to keep the balloon inflated within a given pressure range.

Thawing: Upon termination of the ablation, the system keeps the balloon inflated to allow the surrounding tissue to thaw. When the temperature inside the balloon rises above +20°C, the system deflates the balloon.

The balloon has to be stretched using the push button, located at the back of the catheter handle, to be retracted into the sheath.

4.8.2 Freezor® *MAX* Cryocatheter Operating Mode

The Freezor® *MAX* Cryocatheter procedure involves one operating mode: ablation. When the Freezor *MAX* catheter is positioned in the desired location, the green button on the CryoConsole is pressed to start the refrigerant's injection. A software algorithm controls the pressure set point of the proportional valve in order to reach and maintain a preset flow. The tip electrode can reach temperatures as cold as –88°C. The temperature may vary significantly due to the catheter tip-tissue contact and surrounding blood flow.

The injection of refrigerant can be stopped at any time by pressing on the "Stop Cryoablation" button on the screen or on the red button on the CryoConsole control panel. The catheter is then repositioned and another cryoablation cycle can start. At the end of the pre-set cryoablation cycle, the hardware timer sends a signal that closes the proportionally controlled valve and automatically stops the injection of refrigerant. The catheter re-warms to body temperature which can be verified on the console display.

4.9 Device Development and IDE Chronology

This section provides an overview of the important device development and IDE milestones for Medtronic CryoCath LP cryocatheters for the treatment of paroxysmal atrial fibrillation (PAF). In July 2003, Medtronic CryoCath LP (known at the time as CryoCath Technologies, Inc.) filed an Investigational Device Exemption (IDE) application [G030159] for a "toolbox" of devices to treat PAF, including the Arctic Circler® CurviLinear Cardiac CryoAblation Catheter (for cryoablation of the conducting tissue in or near the os of the pulmonary veins), the Freezor® *Xtra* catheter (for adjunctive cryoablation of linear lesions, gaps in the pulmonary veins, and any focal triggers), and the Freezor® *MAX* Cardiac CryoAblation Catheter [Freezor® *MAX* Cryocatheter] (for creation of a right atrial cavo-tricuspid isthmus cryoablation line). The IDE was conditionally approved for three institutions and 30 subjects on August 28, 2003. This clinical study was termed the ICE-CAFÉ Feasibility Study (PS-009).

Following discussions with FDA on September 20, 2004, Medtronic CryoCath submitted an IDE supplement requesting to:

- Modify the "toolbox" used under the original IDE by replacing the Arctic Circler® CurviLinear Cardiac CryoAblation Catheter with the Arctic Circler® Balloon Cardiac CryoAblation Catheter [Arctic Circler® Balloon] and removing the Freezor® *Xtra* catheter and

- Initiate a feasibility study with the modified "toolbox" in an additional twenty (20) subjects at two centers.

This clinical study was termed the CryoSTOP AF Feasibility Study (PS-012).

After treating 15 subjects with the Arctic Circler® Balloon, Medtronic CryoCath submitted an IDE supplement on October 15, 2005 requesting to:

- Modify the "toolbox" by replacing the Arctic Circler® Balloon Cardiac CryoAblation Catheter with a new device named the Arctic Front® Cardiac CryoAblation Catheter [Arctic Front® Cryocatheter].
- Add the FlexCath® Steerable Sheath [FlexCath® Sheath] to help position the cryocatheters in the heart.
- Initiate a pivotal study of modified "toolbox" in 220 subjects at fifteen (15) US centers.

FDA requested in a letter dated February 2, 2006 for G030159/S27 that the Arctic Front® Cryocatheter be evaluated in an expanded feasibility study prior to initiating a pivotal study with the device. Medtronic CryoCath responded by requesting to expand the feasibility study in order to obtain clinical data on fifteen (15) subjects treated with the Arctic Front® Cryocatheter and CryoConsole. This expanded feasibility study was also called the CryoSTOP AF Feasibility Study (PS-012). Once acute safety and effectiveness and catheter performance data were gathered for these additional subjects (18 subjects were treated), Medtronic CryoCath requested approval for initiating the STOP AF Pivotal Trial (PS-023) under the IDE. FDA granted full approval of STOP AF Pivotal Trial, which included the Arctic Front® Cryocatheter (Models 2AF230 and 2AF280), the Freezor® *MAX* Cryocatheter (Models 239F3 and 239F5), CryoConsole (Gen V) and FlexCath® Sheath, on August 21, 2007 (G030159/S43 and 44). The investigation was limited to 25 sites and 327 subjects.

On February 11, 2008, Medtronic CryoCath met with FDA and proposed a plan to study modified versions of the Arctic Front® Cryocatheter and CryoConsole on crossover subjects[1] from the STOP AF Pivotal Trial. The proposal was approved by FDA on October 3, 2008 in G030159/S58. On November 3, 2008, Medtronic CryoCath submitted a protocol [CAP-AF Continued Access Protocol (PS-024)] requesting to study the modified versions of the Arctic Front® Cryocatheter (Models 2AF232 and 2AF282) and CryoConsole (Modified Gen V also known as Model 106A2) in a continued access study. The CAP-AF Continued Access Protocol (PS-024), which is limited to 100 subjects and 12 sites that had previously enrolled subjects in the STOP AF Pivotal Trial, was granted full approval on April 21, 2009 (G030159/S62 and S63).

---

[1] No crossovers subjects were ever treated with the modified versions of the Arctic Front® Cryocatheter and CryoConsole.

Table 25, v001:p063 below provides an overview of the Cryocatheters and CryoConsoles evaluated under the various studies covered under the IDE G030159. The Arctic Front® Cryocatheter (Models 2AF232 / 2AF282)[2], the Freezor® MAX Cryocatheter (Models 239F3 / 239F5), CryoConsole (Model 106A2) evaluated in CAP AF Continued Access Protocol (PS-024) are the devices that are the subject of the present PMA application. These devices are denoted by **underlined and bolded** font in the table. Please note that the Freezor® *Xtra* catheter and FlexCath® Steerable Sheath while mentioned in the text above are not cited in the table for clarity. Accessory devices such as the Manual Retraction Kit and umbilicals are also not noted in the table

Medtronic CryoCath also sponsored two feasibility studies of cryoablation catheters for PAF in Europe (EU): EU Feasibility Study (PV-ICE; PS-011) and EU Feasibility Study (PV-ICE II; PS-011B). These studies were not conducted under the IDE and are reported in Sections 5.8, v001:p091 and 5.9, v001:p091, respectively.

[2] As noted in Section 2.1.4 of the PMA, an adhesive used to bond the injection tube to the coaxial connector of the Arctic Front® Cryocatheter was replaced. This change was recently submitted (February 2010) as a 5-Day Notice to the IDE G030159. This change was validated on the bench and does not impact clinical performance of the Arctic Front® Cryocatheter.

Table 25 Device Development and IDE Chronology

Device Name / Design	CryoConsole	IDE G030159	Study Name
Arctic Circler® Curvilinear Cardiac CryoAblation Catheter • 7F, Focal curvilinear device; expandable	Gen III and IV	Original IDE 7 / 2003	ICE-CAFÉ Feasibility Study (PS-009)
Arctic Circler® Balloon Cardiac CryoAblation Catheter (Model 2ACB1) • 10F, Non-deflectable, double balloon • Polyimide injection tube • One balloon size: 23mm	Gen IIIB Allows the use of balloon catheters only	IDE/S8 10 / 2004	CryoSTOP AF Feasibility Study (PS-012)
Arctic Front® Cardiac CryoAblation Catheter (Model 2AF230 / 2AF280)	Gen V New software, mechanical updates	IDE/S21 10 / 2005	CryoSTOP AF Feasibility Study (PS-012)
• 10.5F, Bi-directional, deflectable, double balloon • Polyimide injection tube • Two balloon sizes (23 & 28mm)		IDE/S43 and 44 8 / 2007	STOP AF Pivotal Trial (PS-023)
Arctic Front® Cardiac CryoAblation Catheter (Models 2AF232 / 2AF282) • 10.5F, Bi-directional deflectable, double balloon • Nitinol injection tube • Two balloon sizes (23 & 28mm)	**Modified Gen V (Model 106A2)** New software, hardware and mechanical updates to allow the use of focal & balloon catheters	IDE/S60 11 / 2008	CAP-AF Continued Access Protocol (PS-024)
Freezor® MAX Cryocatheter (Models 239F3 / 239F5) • Linear focal catheter • Deflectable with 3 ECG rings	Gen IV and Modified Gen V	IDE and all Supplements	Same cryocatheter used in all studies

5.0 CLINICAL STUDIES

5.1 Introduction

Atrial fibrillation (AF) is a common and disabling cardiac arrhythmia, affecting over 2 million Americans. Pharmacological treatment of AF is unsatisfactory for many patients due to the relatively low efficacy and a high incidence of side effects. The development of trans-vascular radiofrequency catheter ablation techniques have shown considerable clinical promise in the treatment of paroxysmal AF, but are time consuming and have been associated with serious complications. To reduce the complexity of the pulmonary vein (PV) isolation procedure and increase effectiveness, Medtronic CryoCath LP developed a cryoablation balloon designed specifically for pulmonary vein isolation by creating a lesion around the PV ostia.

From 2003 to 2009, Medtronic CryoCath LP (Medtronic CryoCath) conducted a series of clinical investigations of various iterations of cryocatheter devices for the treatment of patients with paroxysmal atrial fibrillation (PAF). Table 26, v001:p066 lists all of the studies and the respective devices evaluated in each study. The Arctic Front® Cardiac CryoAblation Catheter and CryoConsole and Freezor® *MAX* Cardiac CryoAblation Catheter devices that are the subject of the present PMA application are denoted by **underlined and bolded** font in the table.

The ICE CAFÉ Feasibility Study (PS-009), CryoSTOP AF Feasibility Study (PS-012), STOP AF Pivotal Trial (PS-023), and the CAP AF Continued Access Protocol (PS-024) were all conducted under IDE G030159. During the STOP AF Pivotal Trial (PS-023) and the CAP AF Continued Access Protocol (PS-024), several Compassionate Use (United States) and Special Access (Canada) cases were also conducted per applicable regulations. Two European feasibility studies, the EU Feasibility Study (PV-ICE; PS-011) and EU Feasibility Study (PV-ICE II; PS-011B) were not conducted under the IDE. All of the studies are discussed in Section 5.0.

The Arctic Front® Cardiac CryoAblation Catheter System is designed for the isolation of the pulmonary veins from the left atrium by the application of a 23mm or 28mm freezing balloon at the ostium of each pulmonary vein. In conjunction with the FlexCath® Steerable Sheath and the Freezor® *MAX* Cardiac CryoAblation Catheter, this system allows the rapid formation of continuous cryoablation lesions at the PV ostia, the closure of any remaining gaps and the ablation of atrial triggers. The STOP AF Pivotal Trial (PS-023) [Section 5.2, v001:p067] and the CAP AF Continued Access Protocol (PS-024) [Section 5.3, v001:p082] are the studies that provide the primary valid scientific evidence in support of the safety and effectiveness of the Arctic Front® Cardiac CryoAblation Catheter System for the treatment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room -WO66-G609
Silver Spring, MD 20993-0002

Mr. Steven McQuillan
Vice President, Clinical & Regulatory Affairs
Medtronic CryoCath. LP
16771 Chemin Ste-Marie
Kirkland, Quebec H9H 5H3
CANADA

DEC 17 2010

Re: P100010
Arctic Front CryoCatheter System comprising: Arctic Front Cardiac CryoAblation Catheters Models 2AF232 and 2AF282, Freezor MAX CryoAblation Catheter, CryoConsole Gen V Model 106A2, Manual Retraction Kit, and Accessories
Filed: March 12, 2010
Amended: June 16, 2010, June 17, 2010, June 23, 2010, September 7, 2010, and December 2, 2010
Procode: OAE

Dear Mr. McQuillan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the above Arctic Front CryoCatheter System. This device is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 6 months.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you have agreed to provide the following data in post-approval study reports (PAS). Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

You have agreed as described in the draft study protocol provided to conduct a prospective, multi-center post-approval study (PAS), consisting of 300 patients with paroxysmal atrial fibrillation who have failed on medical treatment, to assess the safety and effectiveness of your device in a postmarket setting, in which a representative sample of providers performs the treatment. The study will assess the following endpoints:

1. The proportion of patients free of chronic treatment failure for paroxysmal atrial fibrillation at 1, 2, 3, 4, and 5 years.
2. The proportion of patients free of cryoablation procedure events at 1 year
3. The proportion of patients free of major adverse atrial fibrillation events at 1, 2, 3, 4, and 5 years.

The primary effectiveness hypothesis will be that treatment success will be greater than 45% at three years.

The primary safety hypothesis will be that the frequency of cryoablation procedure events will be less than 14.8% at one year.

The results of this study are to be included in the device labeling (via a supplement to this PMA) when the study is completed.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2).

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/Productsand MedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Shawn Forrest at (301) 796-5554.

Sincerely yours,

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

US006575966B2

(12) **United States Patent**
Lane et al.

(10) **Patent No.: US 6,575,966 B2**
(45) **Date of Patent: Jun. 10, 2003**

(54) **ENDOVASCULAR CRYOTREATMENT CATHETER**

(75) Inventors: **Miriam Lane**, Ste-Anne de Bellevue (CA); **Leonilda Capuano**, Montréal (CA); **David Holtan**, Beaconsfield (CA); **Jean-Pierre Lalonde**, Verdun (CA); **Claudia Lückge**, L'Ile-Perrot (CA); **Jean-Luc Pageard**, Montréal (CA); **Marwan Abboud**, Pierrefonds (CA); **Johnny Al Asmar**, Montréal (CA); **Abderrahim Benrabah**, Pointe-Claire (CA); **Ken Chen**, West Vancouver (CA); **John W. Lehmann**, Wayland, MA (US); **Philippe Marchand**, Hudson (CA); **Robert Martin**, Poughkeepsie, NY (US); **Fredric L. Milder**, Brookline, MA (US); **Daniel Nahon**, Ottawa (CA)

(73) Assignee: **CryoCath Technologies Inc.**, Kirkland (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/945,319**

(22) Filed: **Aug. 31, 2001**

(65) **Prior Publication Data**

US 2002/0045893 A1 Apr. 18, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/378,972, filed on Aug. 23, 1999, now Pat. No. 6,283,959.

(51) **Int. Cl.**[7] **A61B 18/18**

(52) **U.S. Cl.** **606/21**; 606/23; 606/7

(58) **Field of Search** 606/20–26, 7, 606/194; 607/113, 115, 101, 102, 104, 105; 604/96.01, 104

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,246,421	A	9/1993	Saab	604/96
5,273,526	A	12/1993	Dance et al.	604/35

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

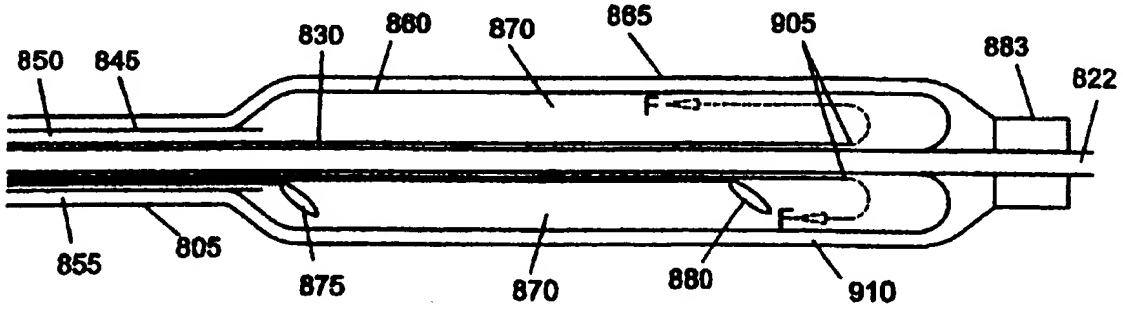
WO	WO9927862	6/1999	

Primary Examiner—Linda C. M. Dvorak
Assistant Examiner—David M. Ruddy
(74) *Attorney, Agent, or Firm*—Christopher & Weisberg, P.A.

(57) **ABSTRACT**

An elongated catheter device with a distal balloon assembly is adapted for endovascular insertion. Coolant injected through the device may, in different embodiments, directly cool tissue contacting the balloon, or may cool a separate internal chamber. In the first case, the coolant also inflates the balloon, and spent coolant is returned to the handle via a return passage extending through the body of the catheter. Plural balloons may be provided, wherein a secondary outer balloon surrounds a primary inner balloon, the primary balloon being filled with coolant and acting as the cooling chamber, the secondary balloon being coupled to a vacuum return lumen to serve as a robust leak containment device and thermal insulator around the cooling chamber. Various configurations, such as surface modification of the balloon interface, or placement of particles, coatings, or expandable meshes or coils in the balloon interface, may be employed to achieve this function.

19 Claims, 9 Drawing Sheets



U.S. PATENT DOCUMENTS

5,484,385	A	1/1996	Rishton	600/16
5,632,762	A	5/1997	Myler	606/194
5,725,521	A	3/1998	Mueller	606/7
5,776,129	A	7/1998	Mersch	606/30
5,827,273	A	10/1998	Edwards	606/41
5,860,971	A	1/1999	Clarke	606/24
5,868,735	A	2/1999	Lafontaine	606/21
5,899,899	A	5/1999	Arless et al.	606/22
5,902,299	A	5/1999	Jayaraman	606/20
5,971,979	A	10/1999	Joye et al.	606/21
6,090,083	A	7/2000	Sell et al.	604/249
6,106,518	A	8/2000	Wittenberger et al.	606/23
6,120,477	A	9/2000	Campbell et al.	604/96
6,290,696	B1 *	9/2001	Lafontaine	606/21
6,368,304	B1 *	4/2002	Aliberto et al.	606/21
6,428,534	B1 *	8/2002	Joye et al.	606/21

* cited by examiner

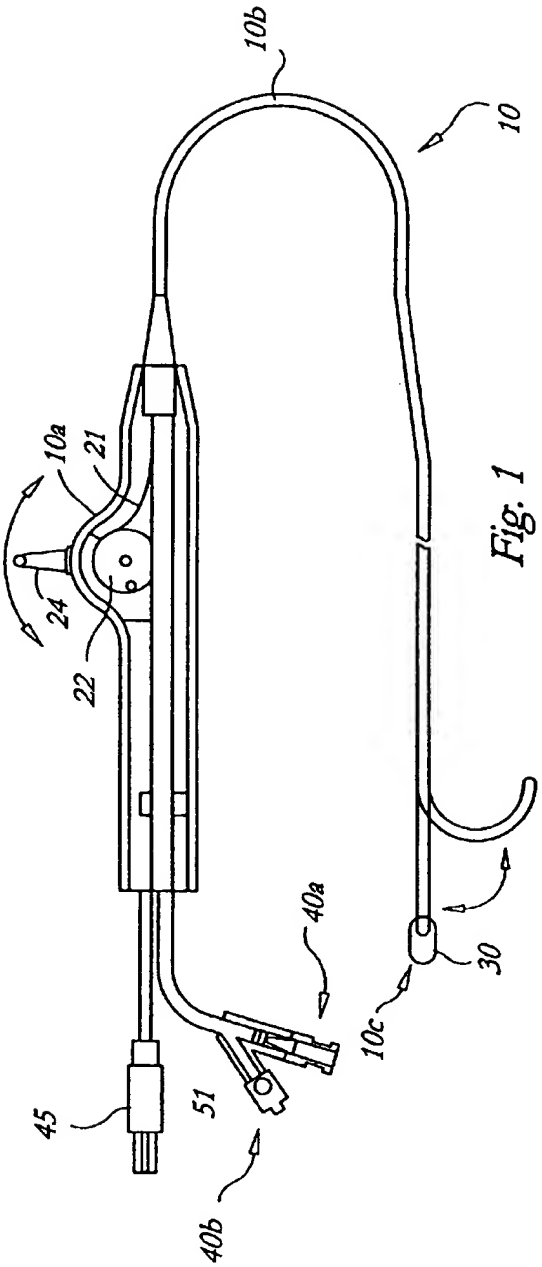

10b
10
10a
21
24
22
40a
30
10c
45
51
40b

Fig. 1

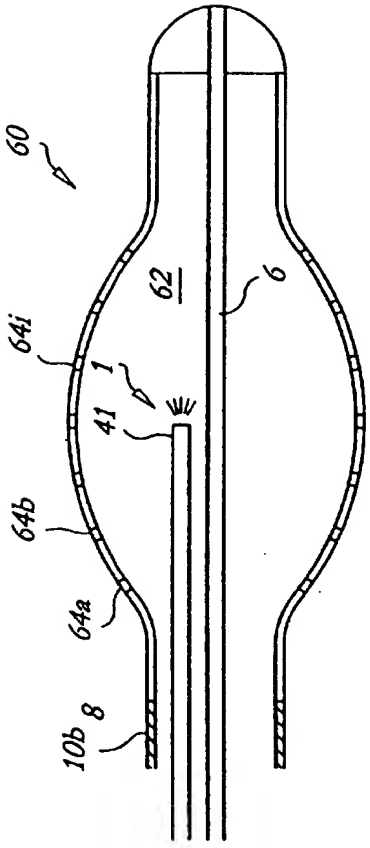

60
62
6
64i
1
41
64b
64a
8
10b

Fig. 2

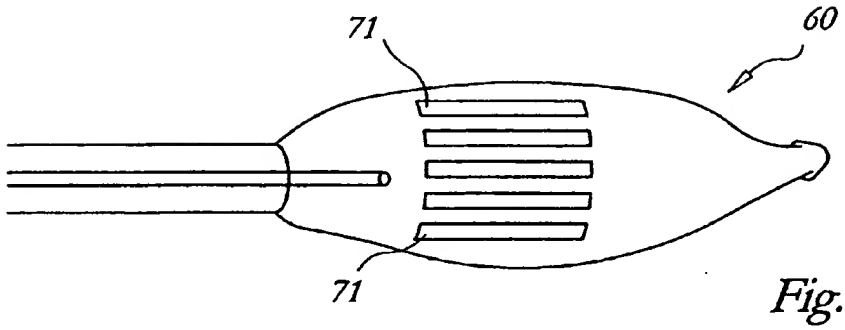


Fig. 3A

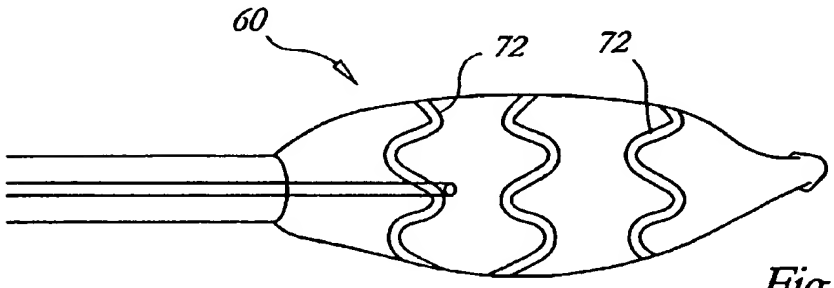


Fig. 3B

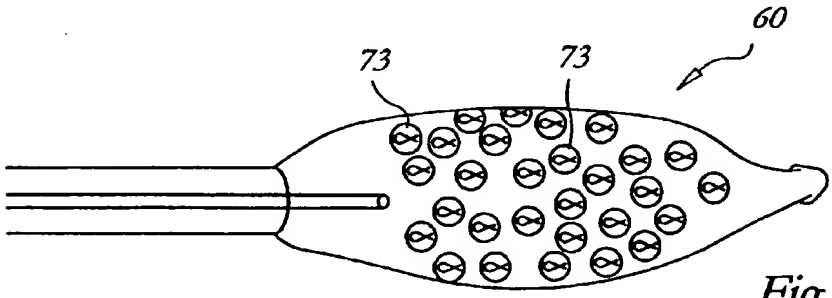


Fig. 3C

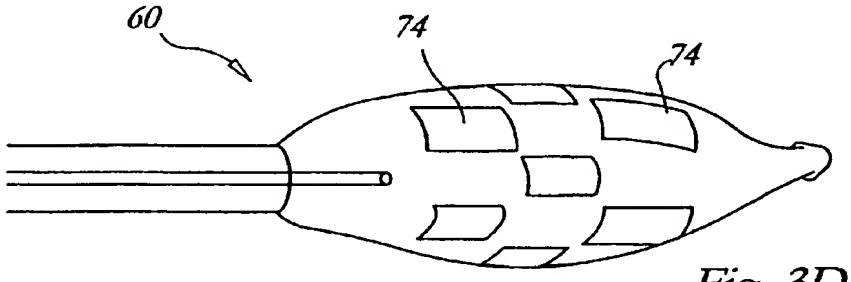


Fig. 3D

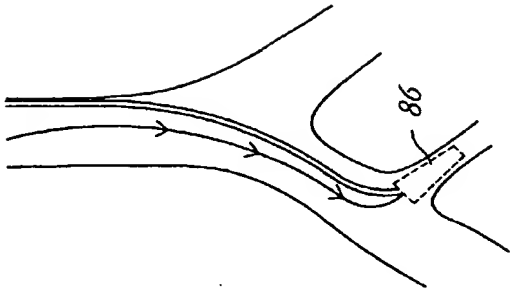


Fig. 5

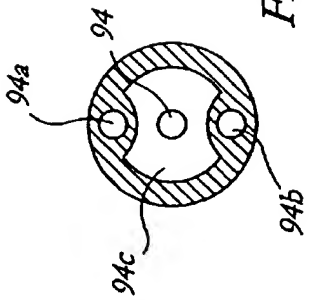


Fig. 7A

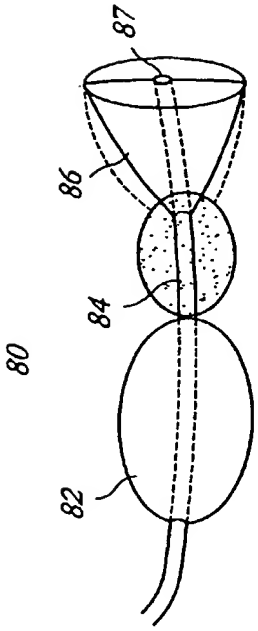


Fig. 4

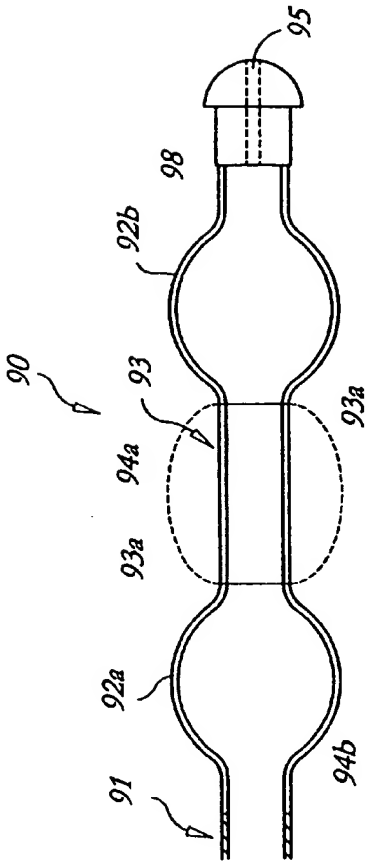


Fig. 7

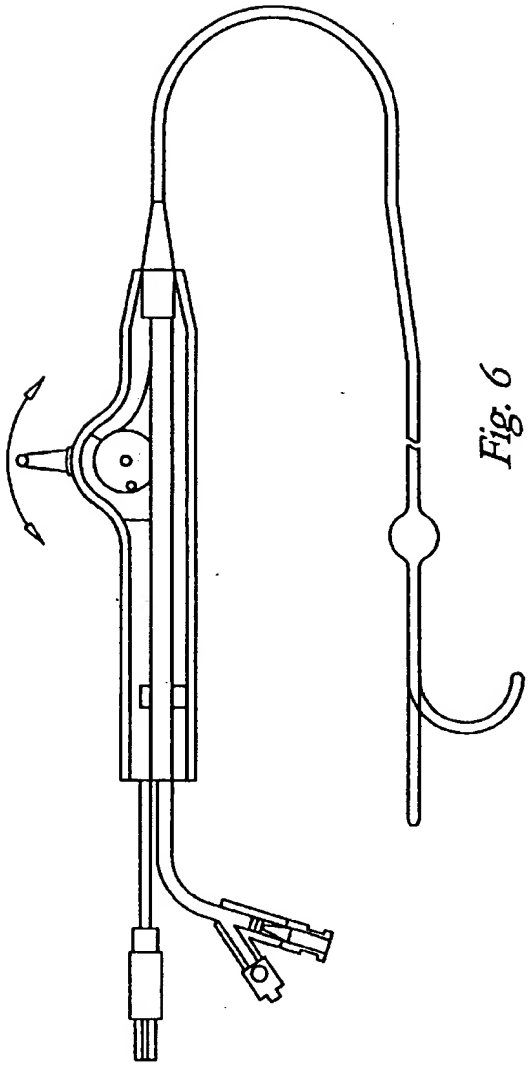


Fig. 6

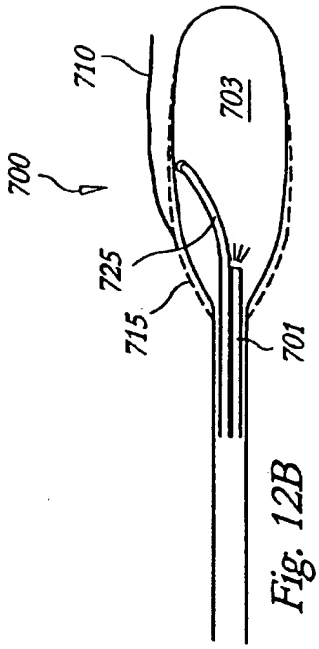


Fig. 12B

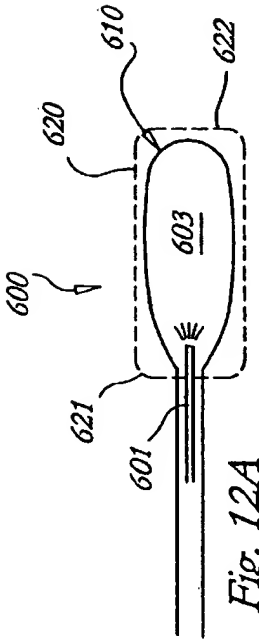


Fig. 12A

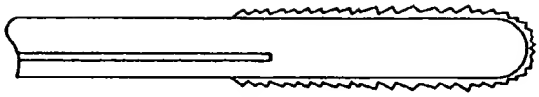


Fig. 8A

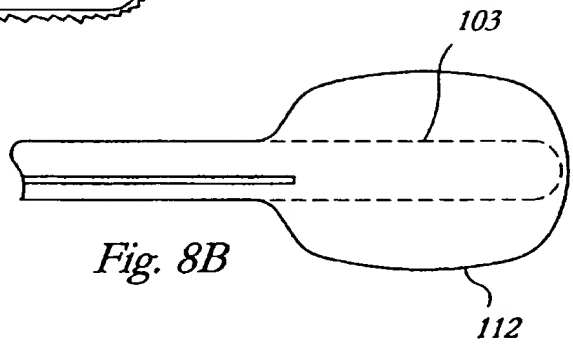


Fig. 8B

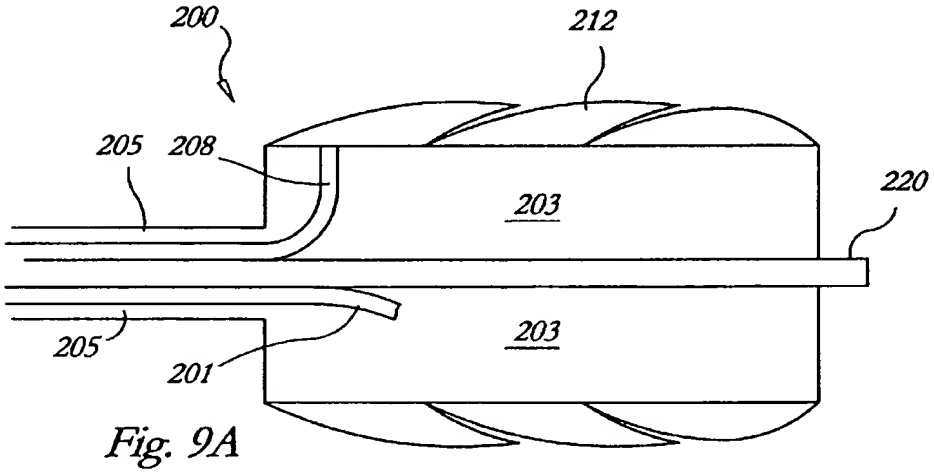


Fig. 9A

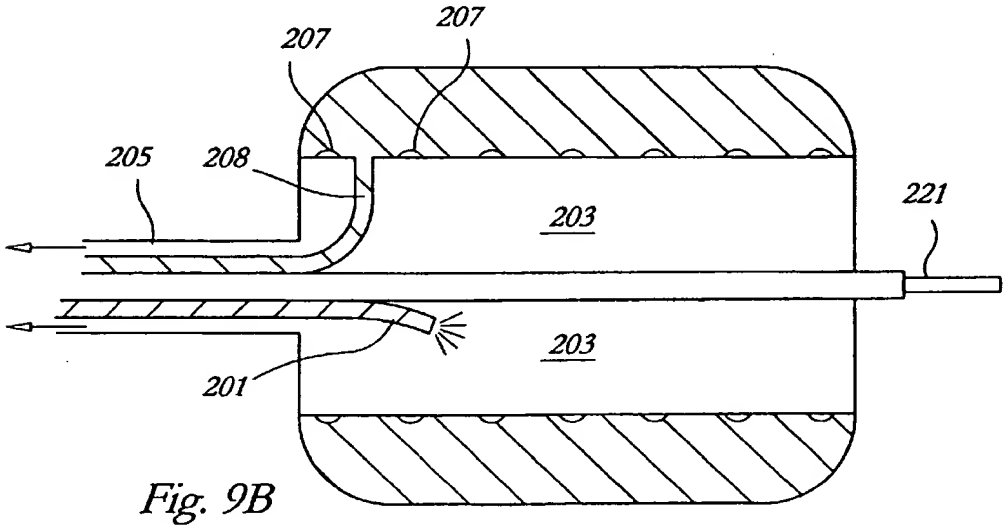


Fig. 9B

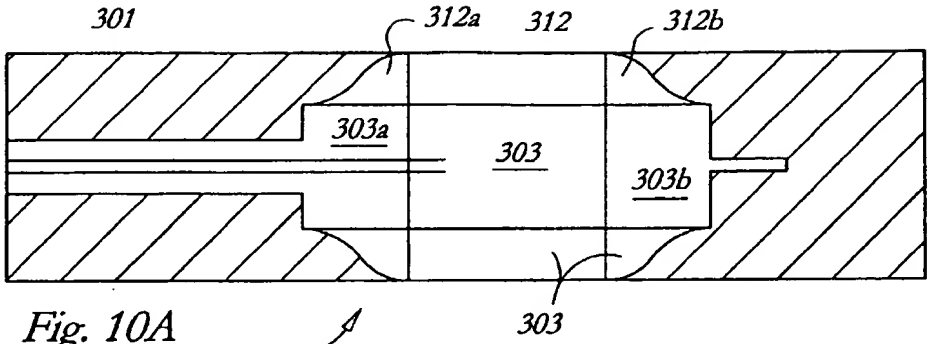


Fig. 10A

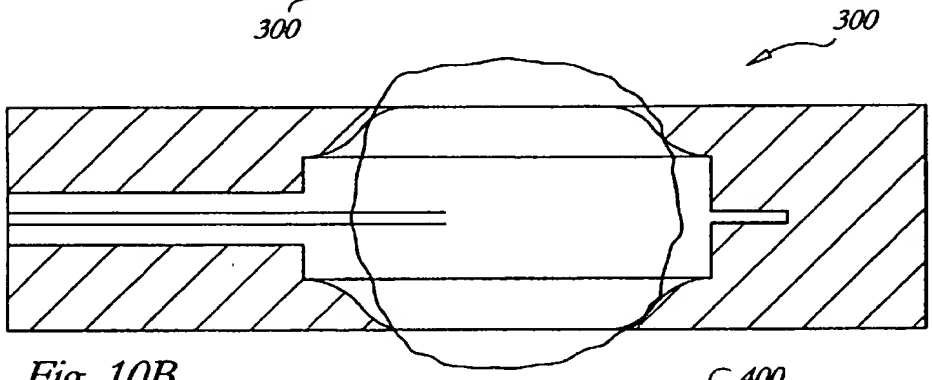


Fig. 10B

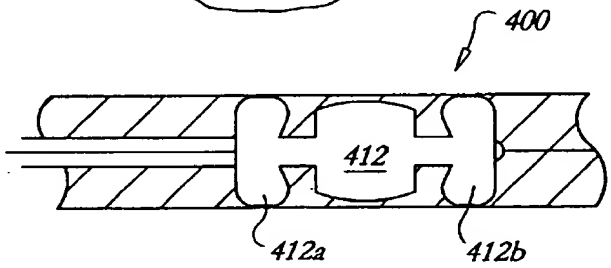


Fig. 10C

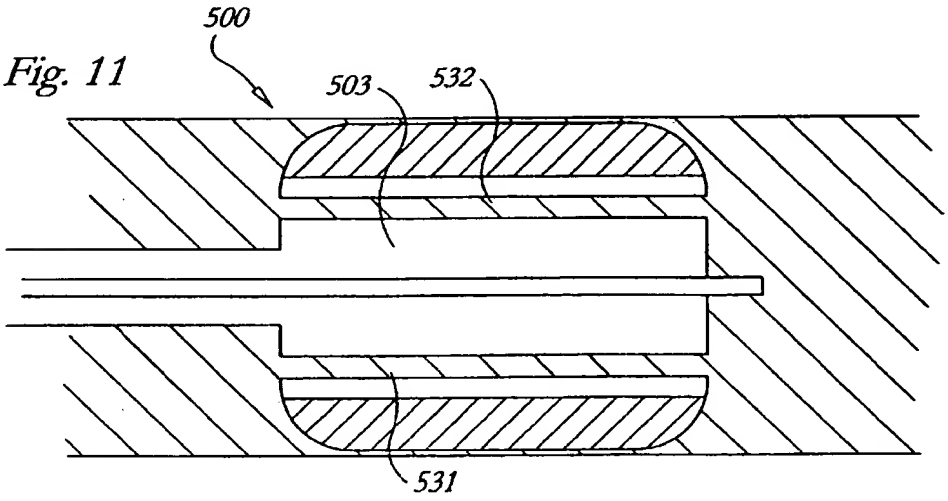


Fig. 11

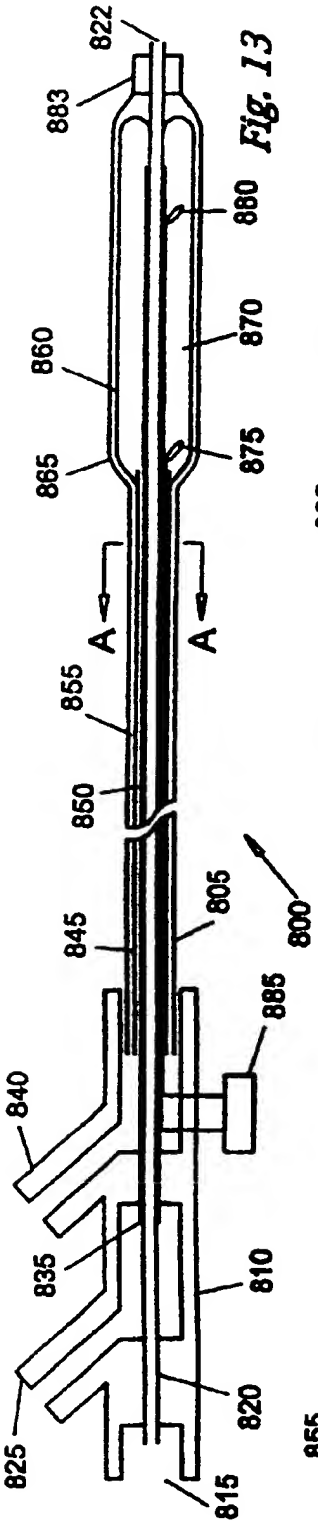


Fig. 13

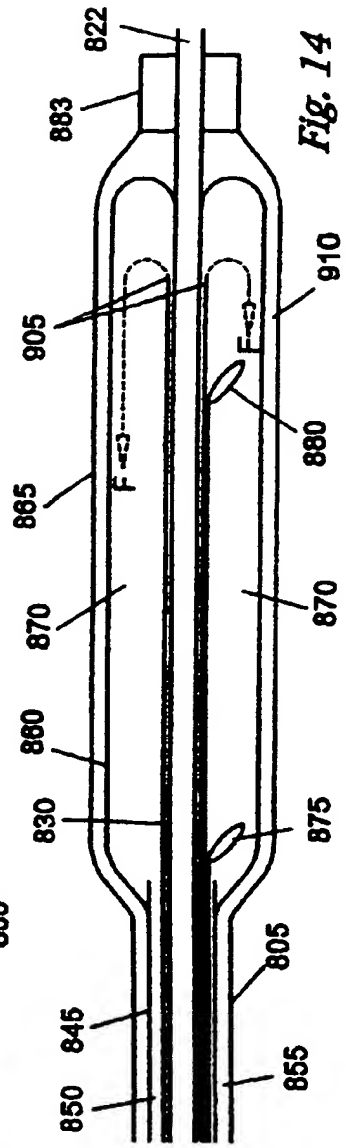


Fig. 14

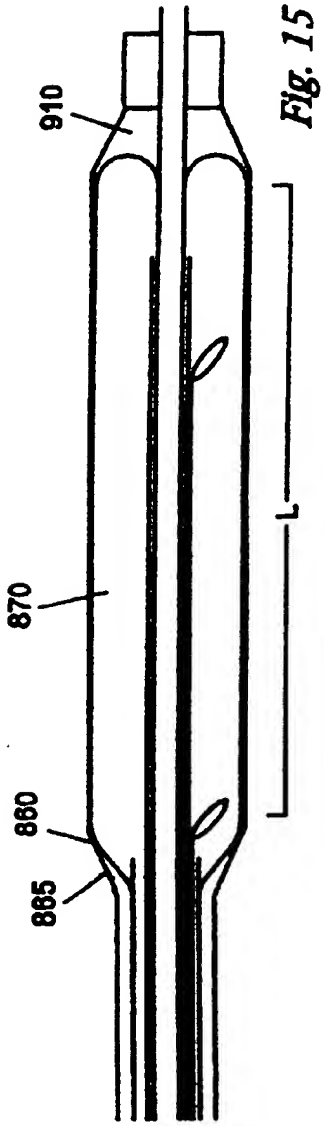


Fig. 15

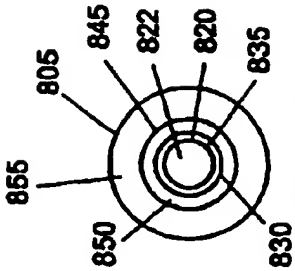


Fig. 13A

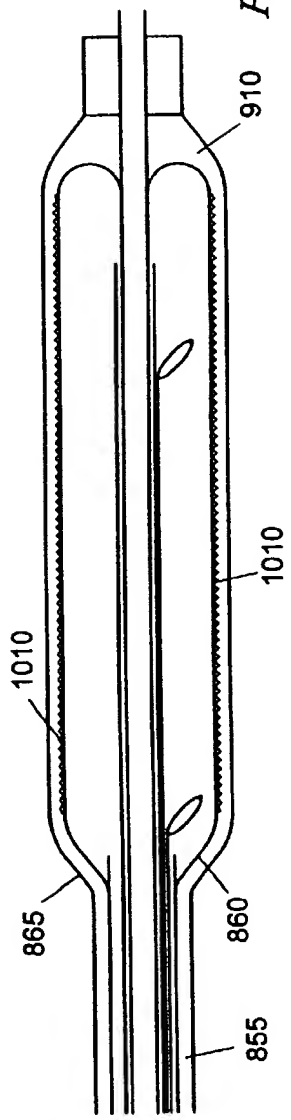


Fig. 16A

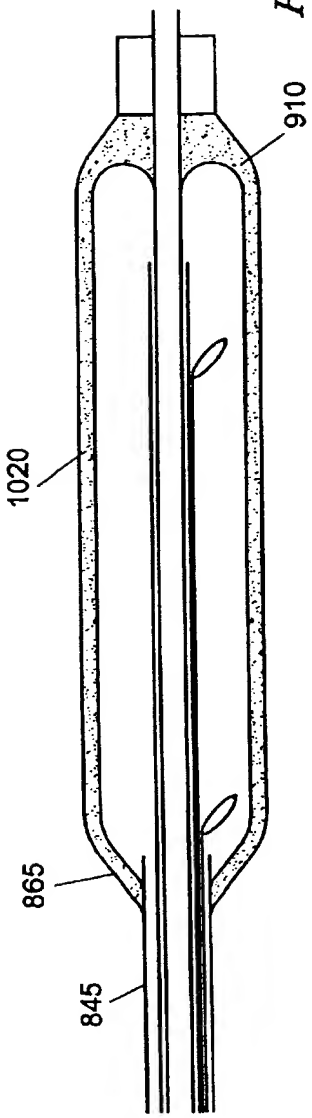


Fig. 16B

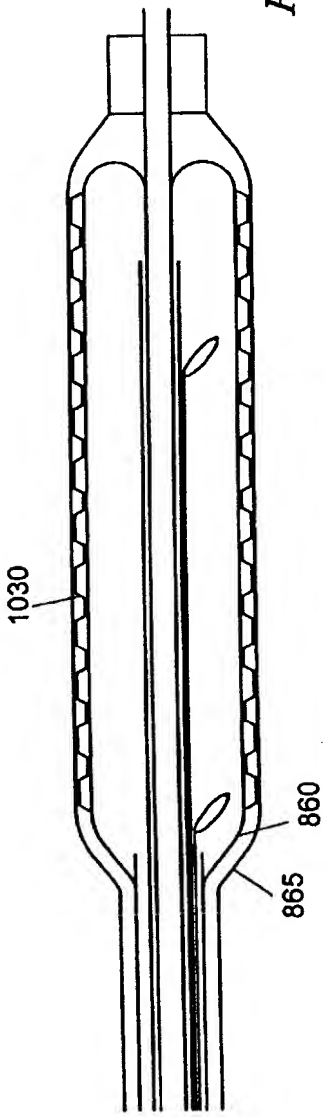


Fig. 16C

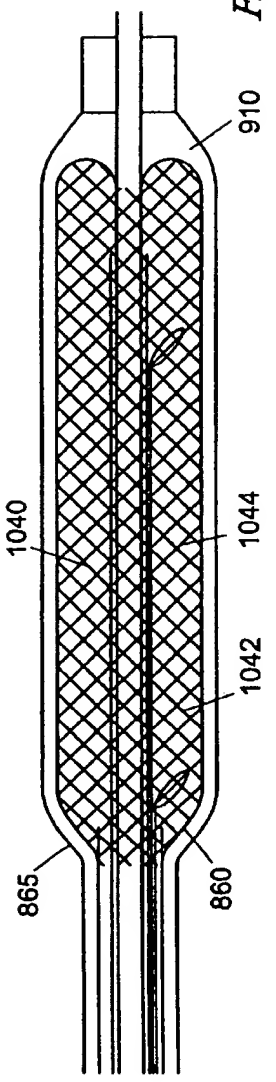


Fig. 16D

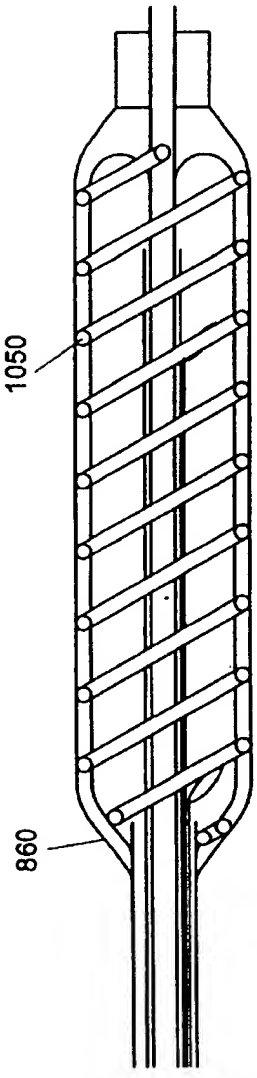


Fig. 16E

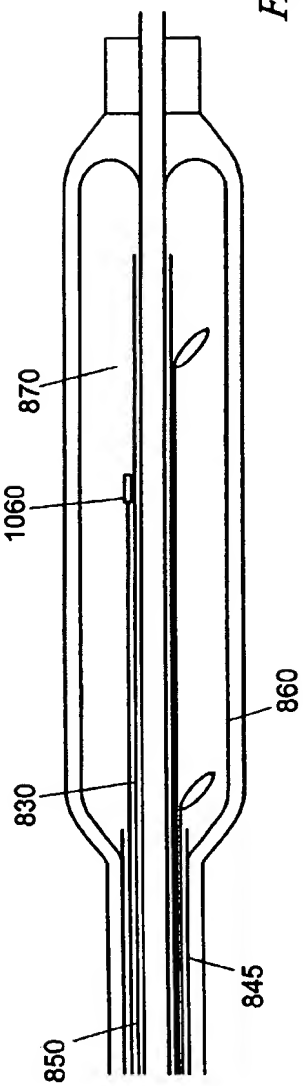


Fig. 17

ENDOVASCULAR CRYOTREATMENT CATHETER

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. patent application Ser. No. 09/378,972, filed Aug. 23, 1999 now U.S. Pat. No. 6,283,959.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

n/a

FIELD OF THE INVENTION

The present invention relates to endovascular catheters, and in particular, to catheters for cryotreatment of tissue.

BACKGROUND OF THE INVENTION

The present invention relates to endovascular cryocatheters, such as angioplasty balloons having a freezing function for treating tissue by extreme cooling contact. These catheters have an elongated body through which a cooling fluid circulates to a tip portion which is adapted to contact and cool tissue. Such a device may include a steering assembly such as an inextensible pull wire and a flexible tip to which the pull wire attaches which may be bent into a curved configuration to aid its navigation through blood vessels to a desired treatment site. When used for angioplasty or the destruction of tissue on the inner wall of a vessel, the catheter generally also has one or more inflatable balloon portions which may serve two functions of displacing blood from the treatment site to allow more effective cooling, and physically distending the affected vessel to break up accumulations of plaque.

Endovascular catheters must be of relatively small diameter, and configured for insertion along relatively confined pathways to reach an intended ablation site. As such, the cooling fluid must circulate through a relatively long and thin body yet apply significant cooling power in their distal tip. The requirement that coolant be localized in its activity poses constraints on a working device. For example, when the catheter must chill tissue to below freezing, the coolant itself must obtain a lower temperature to offset the conductive warming effects of adjacent regions of body tissue. Furthermore, the rate of cooling is limited by the ability to circulate a sufficient mass flow of coolant through the active contact region. Since it is a matter of some concern that proximal, adjacent or unintended tissue sites should not be exposed to harmful cryogenic conditions the flowing coolant must be exposed in a limited region. One approach to cooling uses a phase change refrigerant which is provided through the body of the catheter at relatively normal or ambient temperature and attains cooling only upon expansion within the tip region. One such device treats or achieves a relatively high rate of heat transfer by using a phase change coolant which is pumped as a high pressure liquid to the tip of the catheter and undergoes its phase change expanding to a gas in a small chamber located at the tip. The wall of the chamber contacts the adjacent tissue directly to effect conductive cooling or ablation treatment. Other cryocatheters may employ gas at high pressure, and achieve cooling via the Joule-Thomson effect at a spray nozzle in a cooling chamber at the distal end of the catheter.

In an endovascular catheter as described above, a relatively high cooling power may be obtained. However, the

expansion of a phase change or high pressure coolant exiting from a nozzle within a small catheter tip creates highly turbulent flow conditions. The cooling region of the tip may be implemented as a fairly rigid chamber having highly thermally conductive wall or section of its wall formed for example by a metal shell. However, if one were to replace such a tip with an inflatable balloon as is commonly used for angioplasty, the size of the chamber would vary considerably as the balloon is inflated, causing substantial variations in flow conditions of the fluid entering the tip and substantial changes in heat transport across the expanding balloon wall. Both of these factors would result in variations of the cooling power over the tip. Furthermore, coolant materials suitable for high pressure or phase change refrigeration may pose risks when used within a blood vessel. Accordingly, there is a need for an improved catheter construction for cryogenic angioplasty.

Another factor which adds complexity to the task of cryocatheter design is that the primary mechanism of treatment involves thermal conduction between the catheter and a targeted region of tissue. Thus, not only is the absolute cooling capacity of the catheter important, but the nature and extent of contact between the cooled region of the catheter and the adjacent tissue is important. Effective contact may require moving, positioning, anchoring and other mechanisms for positioning, stabilizing and changing the conformation of the cooled portion of the catheter. Slight changes in orientation may greatly alter the cooling range or characteristics of the catheter, so that even when the changes are predictable or measurable, it may become necessary to provide positioning mechanisms of high stability or accuracy to assure adequate treatment at the designated sites. Furthermore, it is preferable that a vessel be occluded to prevent warming by blood flow during treatment. Beyond that, one must assure that the cooling activity is effective at the surface of the catheter, and further that defects do not cause toxic release of coolant or dangerous release of pressure into the body.

Secondary environmental factors, such as the circulation of blood near or at the treatment site may also exert a large influence on the rate at which therapeutic cooling accrues in the targeted tissue.

There is therefore a need for improved catheter constructions to occlude blood flow and form a dependable thermal contact with a vessel wall.

Additionally, the operation of such a device for therapeutic purposes requires that the coolant be contained within the catheter at all times, lest a leak of coolant enter the body and thereby cause significant harm. Known catheters which employ inflatable balloons often inflate the balloons to relatively high pressures, that exceed the ambient pressure in a blood vessel or body lumen. However, to contain the coolant, these catheters generally employ thicker balloons, mechanically rigid cooling chambers, and other similar unitary construction containment mechanisms. These techniques however, lack robustness, in that if the unitary balloon, cooling chamber, or other form of containment develops a crack, leak, rupture, or other critical structural integrity failure, coolant may quickly flow out of the catheter.

There is therefore, for security purposes, a need for improved cryocatheter constructions to robustly contain coolant flow when cryotreatment is performed.

Finally, a major challenge for effective cryotreatment is the ability to fine tune the pressure and temperature of the coolant flow at the distal tip of the catheter, so as to

controllably apply cooling to adjacent tissue. The cooling power of the device, created through the Joule-Thomson effect and phase change of the coolant as described above, is generally inversely proportional to the resultant coolant pressure achieved after injection into, and during flow through, the cooling chamber or balloon. Thus, in order to maintain the balloon pressure at safe levels, without exceeding ambient body pressures, the device must be operated at relatively lower balloon pressures, which have the undesired effect of raising the cooling power to levels which are difficult to control and may even harm or damage the target tissue. Therefore, the enhanced cooling power of the device achieved under such relatively low operating pressures must be mitigated by providing some form of tunable thermal resistance between the coolant flow and the target tissue.

It is desirable therefore, to provide for an improved catheter system which may safely operate at low balloon pressures while thermally insulating the target tissue from excessive cooling.

SUMMARY OF THE INVENTION

In a first embodiment of the present invention, a body insertable cryotreatment catheter is configured with an elongate catheter body, and distal cooling tip assembly having a cooling chamber surrounded by an expandable member. The expandable member surrounds the cooling chamber to define an interstitial space therebetween. The interstitial space is in fluid communication with a vacuum source. The cooling chamber may be rigid or flexible. A coolant injection lumen is provided in the catheter body such that the cooling chamber is inflatable by the flow of coolant from the injection lumen. Primary and secondary return lumens are in fluid communication with the cooling chamber and interstitial space, respectively, to: (i) define first and second pathways for the flow of coolant, respectively, (ii) contain the coolant flow within the catheter body in the event of structural failure of the cooling chamber, and (iii) to provide supplemental thermal insulation around the cooling chamber. At least one of the inner surface of the expandable member or the outer surface of the cooling chamber may be modified to be topographically non-uniform, so as to provide for a larger interstitial space volume than in the absence of such modification.

In another embodiment of the present invention, a catheter comprises a handle in fluid communication with a supply of cooling fluid having a boiling temperature, a source of vacuum, a cooling chamber having fluid impermeable inner and outer surfaces, and an elongate catheter body having a coolant injection lumen having proximal and distal end portions, the proximal end portion being in fluid communication with the supply of cooling fluid, the distal end portion being in fluid communication with the cooling chamber. The catheter further comprises a primary return lumen having proximal and distal end portions, the proximal end portion being in fluid communication with the source of vacuum, the distal end portion being in fluid communication with the cooling chamber. The catheter also includes an expandable member having inner and outer surfaces coupled around said cooling chamber, wherein a space exists between the cooling chamber outer surface and the expandable member inner surface. Furthermore, a secondary return lumen is disposed within the catheter body, having proximal and distal end portions, the proximal end portion being in fluid communication with the source of vacuum, the distal end portion being in fluid communication with the space.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete understanding of the present invention, and the attendant advantages and features thereof, will be more readily understood by reference to the following detailed description when considered in conjunction with the accompanying drawings wherein:

FIG. **1** illustrates a balloon catheter system in accordance with a first embodiment of one aspect of the present invention;

FIG. **2** shows a cross section taken along the axial direction through the balloon portion of another embodiment of the invention;

FIGS. **3A–3D** illustrate four embodiments of thermally conductive balloons in accordance with the invention;

FIG. **4** illustrates another embodiment of the invention;

FIG. **5** illustrates balloon orientation;

FIG. **6** illustrates an embodiment with proximal anchoring/occlusion balloon;

FIG. **7** illustrates another two balloon cryocatheter;

FIG. **7A** illustrates a section through a multilumen catheter suitable for the practice of the invention;

FIGS. **8A** and **8B** show another balloon embodiment of the invention in its deflated and inflated state, respectively;

FIGS. **9A** and **9B** show a balloon embodiment with separate cooling and inflation media;

FIGS. **10A–10B** show yet another balloon embodiment;

FIG. **10C** illustrates a further variation on the embodiment of FIGS. **10A–10B**;

FIG. **11** illustrates another embodiment;

FIGS. **12A** and **12B** illustrate delivery embodiments;

FIG. **13** shows a cross section taken along the axial direction of a dual balloon catheter system;

FIG. **13A** illustrates a transverse cross-section of the catheter body along lines A—A in FIG. **13**;

FIG. **14** illustrates a cross section taken along the axial direction through the distal portion of the catheter system of FIG. **13**;

FIG. **15** illustrates the catheter system of FIG. **14**, when the outer balloon is under vacuum pressure;

FIGS. **16A**, **16B**, **16C**, **16D**, and **16E** illustrate various alternative embodiments of the catheter system of FIG. **14**; and

FIG. **17** shows the catheter system of FIG. **14** with a pressure transducer located in the inner balloon.

DETAILED DESCRIPTION OF THE INVENTION

FIG. **1** illustrates a treatment catheter **10** in accordance with a basic embodiment of the present invention. Catheter **10** includes a handle **10***a*, an elongated intermediate body portion **10***b*, and a distal end **10***c*. An inextensible guide wire **21** extends from the handle to the tip **10***c* for exerting tension via a take up wheel **22** that is turned by lever **24** to curve the tip of the catheter and steer it through various branch points along the route through a vessel to the intended treatment site. Alternatively, the catheter may be provided with a central guide wire lumen. In that case, a guide wire is inserted into the vessel up to or past the treatment site and the catheter is then placed over the guide wire. As further shown in FIG. **1**, a balloon **30** is attached to the distal end of the catheter and as described further below is in communication via the intermediate body **10***b* and handle **10***a* with an inlet **40***a* for the refrigerant fluid, and an outlet **40***b* through which spent refrigerant returns. The handle may also receive electrical connections via a port or cable **45** for various sensing or control functions described further below.

General principles concerning the construction or operation of such a cryocatheter may be found in U.S. Pat. No. 5,281,215 which is incorporated herein by reference for purposes of disclosure and illustration.

In accordance with one aspect of the present invention, the refrigerant fluid applied at the port **40***a* is applied through a first passage to the balloon and returned from the balloon through a second passage to the outlet **40***b*, at a positive pressure. For example, a valve may be present downstream of the balloon to set a back pressure which effects inflation of the balloon by the coolant fluid. As illustrated in FIG. **1**, the valve may be implemented by a check valve **51** positioned at the port **40***b* and set for example to open at a pressure of 10 psig to maintain a sufficient back pressure in the return line for inflation of the balloon **30**. In alternative embodiments, the check valve **51** may be replaced by a controllable valve, or a pressure sensing arrangement that provides a feedback signal in conjunction with an electrically controlled valve, to assure that the desired inflation pressure is achieved at the balloon **30** while allowing return of coolant continuously through the outlet **40***b* to a control console. In either case, the return valve maintains a minimum pressure at the outlet side of the catheter assembly. This minimum pressure is at a level higher than blood pressure to assure that the balloon inflates and occludes the vessel in which it is located.

In one embodiment, a relatively thin balloon is placed at the end of the catheter and is folded over the shaft so that when the coolant fluid is injected, the balloon opens and inflates to occlude blood flow within the vessel where it is situated. By increasing the injection pressure to the balloon, the rate of cooling is increased to apply cryogenic conditions at the surrounding wall of the vessel. Preferably, a refrigerant such as liquid CO_2 is employed having relatively controllable thermal characteristics for the desired treatment range. Leakage of CO_2 into the blood stream, if it occurs, is harmless in small amounts. This construction may be varied somewhat. For example, the balloon may be a relatively thick-walled balloon intended when inflated to exert mechanical force against the vessel wall to break up plaque. In that case, relatively higher inflation pressures are used, and the outlet valve **51** may be operated to maintain back pressures up to several atmospheres or more. Furthermore, it will be understood that the relatively small cross-sectioned opening present in the body **10***d* of the catheter may itself operate to cause a pressure drop, or back pressure, so that the valve **51** may be set to a lower opening pressure threshold, so long as back pressure at the balloon is maintained sufficiently high in the range for balloon inflation.

In accordance with one aspect of the present invention, the balloon operates to treat adjacent vascular tissue by freezing.

This is achieved in one preferred aspect of the invention by a balloon fabricated with a wall metallization that enhances the heat transfer rate through all or a portion or pattern of the balloon wall. FIG. **2** is a cross-sectional view through one such balloon **60** taken in a plane along the axis of the device. As shown, the balloon **60** is attached to the end of the catheter shaft **10***b* and has a refrigerant injection tube **4** extending to its interior so that refrigerant flows out the end or other apertures which are provided in the distal portion of the tube **4** and fills a chamber **62** defined by the interior of the balloon. A guide wire lumen **6** may extend to the distal tip for facilitating insertion, and a steering wire (not shown) may be positioned in the adjacent portion of the tip or extend through the balloon, in a manner generally known in the art of catheter design to deflect the tip portion. Within the body of the catheter shaft lob, the region of the lumen not occupied by the injection tube and other described components serves as a return passage for the refrigerant released from the nozzle end **1** of the injection tube **4**. As further shown in FIG. **2**, the balloon **60** has a wall of membrane thickness with a pattern of metallization, visible as metal regions 64_a, 64_b . . . 64_c disposed over its surface. The patterned metallization regions **64** have higher thermal conductivity than the bulk balloon membrane material, and define regions at which destructive freezing contact to the vessel wall itself will occur when the balloon is inflated.

FIGS. **3**A through **3**D illustrate various patterns suitable for use in the present invention in perspective view on a representative balloon **60**. As shown in FIG. **3**A, one such pattern includes a plurality of substantially axially oriented lines **71** disposed around the circumference of the balloon. The balloon is shown in a partially inflated posture. When inflated more fully, the balloon expands and the lines **71** move apart around the circumference. Since expansion occurs only in the radial direction, the metal does not constrain expansion of the balloon or introduce localized stresses or cracking during expansion.

FIG. **3**B shows a second useful pattern in which the conductive pattern include a zigzag or meandering arrangement of conductive metal portions **72** configured such that bends or junctions of successive path region allow the balloon to expand without constraint. In this case, radial enlargement and circumferential expansion of the balloon wall simply bends the metal paths. In general, any of the shapes which have been found suitable for expanding metal mesh, wire or coil stents may be useful as surface patterns for the balloon membrane to enable it to undergo radial expansion without introducing mechanical faults into the balloon membrane.

The invention also contemplates conductive patterns in which the conductive regions consist of a plurality of substantially separated or disjoint small loci. These may consist of solid regions such as dots **73**, or squares or rectangles of relatively small overall extent, e.g., under several millimeters across, to produce dimpled regions of conduction extending over the whole surface of the balloon as shown in FIG. **3**C, or may include one or more large areas so as to adapt the balloon for applying a particular pattern of localized cooling, such as a cooling through on side of the balloon while still allowing the balloon to expand in its entirety to firmly lodge the balloon within the vessel and displace blood so as to allow the cooling surface of the balloon to effectively and directly contact the vessel wall.

FIG. **3**D shows another useful pattern **74** for the balloon.

The metal or conductive regions **71**, **72**, **73** and **74** may be applied using lithographic printing technology, for example, by applying a metal-loaded thermally conductive ink in a polymer base to the membrane, or by applying complete coatings and patterning and etching away regions by lithography techniques to form the desired pattern. Such patterns may also be formed by applying a metal foil layer or depositing such a layer by plating or sputter deposition techniques and employing lithographic methods to pattern the continuous layers. In general the pattern is formed so as to create a desired pattern of icing lines for effectively destroying tissue at the patterned areas of conductive contact when the balloon is inflated. The conductive regions **64**, **71**–**74** may also be created by adding thermally conductive materials such as copper powder, flakes or fibers to the material of the balloon membrane itself. In that case the powders or fibers are preferably mixed with the appropriate

elastomer or polymer material from which the balloon is to be formed, and the balloon is then formed by a known technique such as molding, forming on a mandrel, dipping or other common balloon forming technique. When patterning is desired, a standard elastomer and a conductively loaded elastomer may be painted on in bands or otherwise patterned during the manufacturing process to create the desired thermal contact regions.

FIG. **4** illustrates another embodiment **80** of the present invention. This embodiment has a multi-balloon structure and a cooling segment **84** at the catheter tip. As illustrated, segment **84** corresponds to the expansion chamber or region of greatest cooling activity of the catheter and includes a cooling pattern assembly. This may be a spiral metal wrapping that provides stiffness, form and thermal conductivity to the segment. A first balloon **82** is positioned on one side of the cooling segment **84** to serve as an anchor and blood vessel occluder or flow blocker, and in this embodiment a second balloon **86** extends from the other end of the cooling segment. As shown, the first balloon is substantially ovaloid and symmetrical, while the second balloon **86** has a tapered, trumpet-or bell-shaped aspect that allows it to wedge at the end of a vessel, for example, in the ostium or junction of the vessel end to an organ. Thus, while the balloon **82** is inflatable within a vessel to serve as an anchor, balloon **86** is adaptable to fit in an opening and occlude the opening, or define an end-contact geometry for positioning the cooling segment **84** in close proximity to the vessel end opening.

It will be appreciated that the cooling segment **84** in this embodiment has a relatively fixed diameter and is not subject to inflation. Rather it has high thermal conductivity and in use when actuated by flow of refrigerant within the catheter, an ice ball forms to extend its thermal range. The region of ice formation is indicated schematically by the external dotted profile positioned around the cooling segment of the catheter.

As further shown in FIG. **4**, the catheter assembly may include a guide wire lumen **87** for over-the-wire insertion, or for monorail guiding movement of the distal tip. Alternatively, the distal termination may include a conventional wiggler tip or a steering assembly manipulated from the handle end of the catheter. Furthermore, the positions of the balloons **82** and **86** may be interchanged, with the anchor balloon **82** being positioned distal to the cooling segment **84** and the tapered or trumpet balloon **86** positioned proximally thereof. This configuration allows use of the catheter by insertion along the opposite direction of the vessel, for example, through a cardiac chamber and into a vessel exiting the chamber.

Thus, in accordance with this aspect of the invention, the cryocatheter includes a cooling segment that is positioned and anchored by one or more occlusion balloons. Preferably at least one of these balloons is inflated with the carbon dioxide or other biocompatible refrigerant from the cooling segment. The balloons are not necessarily of equivalent dimension, geometry or compliance. The anchoring balloon may be inflated via an individual inflation lumen, thus allowing the position to be precisely set and this balloon inflated before cooling is initiated. The tapered balloon may be inflated in multiple ways depending on the desired effect. For example, when it is desired to treat a lesion in a vessel in close proximity to the ostium, for example, in the renal arteries, the catheter may be configured such that the coolant both inflates and cools the balloon **86**, so that its tapered surface is a contact cooling surface for treating the adjacent vessel tissue.

In another embodiment, an individual inflation lumen may be provided for the flared balloon **86**. In that case, this balloon may be inflated first when it is desired, for example, to place the cooling segment **84** in close proximity to the ostium. Balloon **86** may then serve the function both of positioning the cooling segment, and of occluding blood flow in the treated region. Thus, the catheter of FIG. **4** may be used for cryogenic treatment in a blood vessel and is well adapted to forming lesions near or at the ostium of the vessel. As noted above, by reversing the positions of balloons **82** and **86**, the catheter may be navigated from the opposite direction along a vessel to treat a site near a junction. Furthermore, by reversing the taper orientation of the balloon **86**, the catheter may be configured to more effectively treat a junction of particular size and accessible from one orientation.

In yet another embodiment, the catheter is manufactured without the symmetric anchoring balloon **82** and carries only the cooling segment **84** and trumpet balloon **86** at its tip, forming a configuration for making relatively linear lesions in locations where the vessel diameter changes rapidly. For example, such a modified catheter may be used for treatment in an antegrade approach to a treatment site along the femoral artery, as shown in FIG. **5**.

FIG. **6** shows another embodiment of the invention. This embodiment is similar to that of FIG. **1**, but the catheter tip is configured so that rather than applying cryogenic cooling through an expandable balloon, the cooling segment is of substantially fixed diameter, which may be comparable to that of the catheter body, and it extends distally from a proximal balloon which functions to occlude the blood vessel in which the catheter lies. As shown, the tip portion is deflectable by means of a tension wire connected to the handle, so as to more effectively navigate along vascular branching passages. The tension wire may also be operated to urge the cooling segment into contact at the intended target site. As in the embodiment of FIG. **1**, the coolant is preferably liquid carbon dioxide, and the coolant return line is kept at a pressure higher than the nominal blood pressure in the vessel being treated. The balloon may thus communicate with the return flow of gas so that the returning coolant inflates the balloon and effectively occludes the vessel. By placing the balloon sufficiently far downstream from the cooling segment or liquid expansion opening, the return gas may be warmed sufficiently to avoid freezing tissue in the balloon occlusion region. Similarly, by locating the balloon closer to the freezing segment, the cooler carbon dioxide will provide cryogenic treatment through the balloon surface to an additional region of tissue adjacent the cooling segment. In further embodiments, a distal balloon (not shown) may also be provided. A limiting orifice is preferably placed in the catheter lumen between the coolant injection tube and the distal balloon to prevent cold gas from entering the balloon too rapidly. Thus, the distal balloon is trickle-filled from the expansion region of the catheter to provide dependable occlusion or anchoring without damaging surrounding tissue.

In any of the foregoing embodiments, applicant contemplates that a valve release, or an actively-switched vacuum connection may be provided to quickly deflate the balloons on demand by reducing back pressure of the return lumen in the catheter body.

FIG. **7** shows another embodiment **90** of the invention, illustrated by way of an axial cross-section taken in a diametral plane through the tip of the catheter. As shown, the tip of the catheter includes a pair of balloons **92***a*, **92***b* surrounding a cooling segment **93**. As shown, the cooling segment and balloons may be formed by a common cylindrical membrane surrounding the catheter body, while the

elongated catheter body provides necessary lead in and return passages for inflation of the balloons and delivery of cooling fluid. The cooling segment possesses a heat exchanging surface **93***a* which may also be a metallic or structural component of the device. For example, the surface indicated by elements **93***a* in the Figure may be formed by a metal spring surrounding the body, or by a metal coating or foil lithographically etched to form a coil embedded in or surrounding the membrane. Alternatively, or in addition, the cooling segment may be implemented by a helically slotted coolant supply tube fixed in the lumen of the catheter shaft to preferentially direct the coolant in liquid form against the wall of the coolant segment. In this embodiment, the catheter shaft **91** is preferably a multilumen shaft, implemented as shown, for example, in FIG. **7**A. The lumena may include, in addition to a guide wire lumen if one is provided, a lumen **94** for coolant delivery, a larger return lumen **94***c* which may surround the delivery lumen, and one or more auxiliary lumens **94***a*, **94***b*. In various embodiments the auxiliary lumens are connected via the handle to separately inflate one or more of the balloons **92***a*, **92***b*. Alternatively, when balloon inflation is performed by trickle inflation of gas from the cooling segment **93**, an auxiliary lumen may be used for a controllable vacuum passage which is actuated to deflate a balloon. As noted above, inflation of the balloons may be effected by the spent or warmed phase change coolant gas in its course towards the return lumen.

When balloon inflation is entirely effected by gas from the cooling segment, one or more of the lumena may be used to contain a steering wire or other accessory unrelated to fluid transfer. Thus as illustrated in FIG. **7**, the catheter **90** may be configured with a guide wire lumen **95** for navigation within a vessel, or may include a steering and support wire assembly **98** within the catheter body to aid insertion. The invention also contemplates that, in a manner similar to the embodiments described above, the catheter **90** may be implemented with a single occlusion balloon, which is preferably placed proximal to the cooling segment for antegrade approaches to lesion treatment. Alternatively, the balloon may be placed distally of the cooling segment when it is desired use the device for treating lesions by a retrograde approach. When both occlusion balloons **92***a*, **92***b* are present, the cooling segment is readily anchored in short, branched or turning passages by inflating one or both balloons. The balloons may further be of different sizes or may be shaped as discussed above for particular applications and vessels.

In addition to the specific embodiments discussed above, in one aspect of the present invention, the invention include a balloon disposed as an annular chamber or cuff around a cooling assembly. Such an embodiment is shown in FIGS. **8**A and **8**B. In accordance with this aspect of the invention, the catheter **10** carries a coolant injection tube **1** which extends to a cooling chamber structure **103** that is surrounded by a cooling balloon **112**. The cooling chamber structure **103** is relatively stiff or even rigid and has substantially fixed dimensions. It may be implemented, for example with a cylinder formed of hard polymer or metal and having a fixed diameter. Surrounding the cooling chamber cylinder **103** is a balloon **112** shown in its deflated state in FIG. **8**A and shown fully inflated in FIG. **8**B. When the cooling and balloon inflation are carried out by the same medium, the cooling chamber **103** may be implemented with a perforated chamber wall. The use of a substantially rigid chamber **103** allows the coolant flow upon exiting the injection tube to undergo substantially regular conditions and therefore provides well regulated and predictable cooling characteristics. However, the invention also contemplates that the balloon may be inflated with a pressurizing medium other than that provided by the refrigerant. In either case the balloon may be formed of a quite thin membrane, on the order of 0.02 millimeters thickness or less, so that in this case it presents very little impediment to heat conduction.

In this construction, the balloon serves as a compliance member to conform to irregular tissue surfaces, and may be used to apply pressure to a lumen to enlarge the lumen in a manner similar to that employed in coronary angioplasty and fallopian tuboplasty procedures. The balloon may also be operated to occlude blood flow when used in an endovascular catheter for rapid therapy since the inflation portion may be deployed or deflated substantially instantaneously. The balloon further operates to center the cooling chamber within the lumen, thus assuring substantially concentric cooling characteristics for the treatment. Finally, the balloon serves to anchor the cooling chamber in position.

The provision of a fixed dimension cooling chamber surrounded by an annular balloon that is inflated by a separate medium, advantageously provides an enhanced spectrum of operating characteristics. Several examples follow illustrating the range of this construction of the invention.

FIGS. **9**A and **9**B schematically illustrate the construction of a guide wire cryocatheter **200** having such a circumferential cushioning balloon **212**. This construction may also be applied to cooling other cylindrical tissue structures or body lumens, including organs or structures such as the fallopian tube, esophagus, biliary duct, ureter, gastrointestinal tract and the bronchus. For each of these different applications, the relative diameter of the cooling chamber and the thickness of balloon portion may be varied so as to achieve for example high total cooling with a large cooling chamber and an effective rate of heat transfer from the surrounding tissue area through a relatively thinner layer of cooling balloon. Notably, the balloon may inflated with a medium such as precooled saline solution having a high rate of thermal conductivity and a high thermal storage capacity, to achieve quick chilling and to maintain a stable thermal set point without having to design the cooling chamber to bear the full thermal load alone.

As shown in FIG. **9**A, the injection tube **201** enters the expansion chamber **203** and injects refrigerant at high pressure, which then expands in the chamber and is exhausted through the exhaust lumen **205** which constitutes the major portion of the catheter shaft. The balloon **212**, shown in its collapsed state in FIG. **9**A around the circumference of the cooling chamber, is inflated via a balloon inflation lumen **208**. Applicant contemplates that the balloon inflation may be effected by a number of inflation media, including a gaseous coolant medium from the other (coolant) chamber **203**. However, preferably, in this embodiment an incompressible liquid such as saline solution having a high thermal capacity and excellent heat conductive properties is applied through the inflation tube **208** to fill the balloon as shown in FIG. **9**B. The external surface of the expansion chamber **203** may be provided with texture, such as a plurality of isolated bumps or dimples **207**, of which several are shown in cross-section, to provide unobstructed fluid percolation passages along the surface and assure that the balloon inflation fluid may have free access and flow quickly to and from the passage **208**. This allows the balloon to fully deflate when fluid is withdrawn via passage **208**.

A guide wire lumen **220** passes centrally through the cooling chamber assembly and as shown in FIG. **9**B accom-

modates a guide wire **221** for directing and positioning the catheter. As further shown in those Figures, the outer diameter of the cooling chamber may extend for a relatively great portion of the total diameter of the device so that the balloon portion occupies only a thin shell which effectively extends the reach of the cooling chamber and provides a short heat conduction path together with firm compliant contact with surrounding tissue. As noted above, when used for angioplasty and other cryogenic treatment contexts the balloon serves to apply a stretching or extensile force to tissue, which is conducive to the desired tissue treatment destruction or regeneration process. The provision of such enlarged cooling chamber also provides a greater external surface area for the coldest central structure of the catheter, greatly enhancing the rate of thermal transfer achieved with the balloon assembly.

In general the body of the catheter may be comparable to that of existing treatment devices, e.g., one to four centimeters in length for an endovascular angioplasty device. However the cryogenic portion need not extend the full length of the tip assembly, and the structure may include axial extension portions which are not cryogenically cooled.

FIGS. **10**A through **10**C illustrate a construction of a cryocatheter **300** of this type. In this embodiment, the tip of the catheter includes chambers **303**, **303***a* and **303***b* all located within the balloon. The chamber **303** serves as a cooling expansion chamber in the manner described above, and the cooling injection tube **301** opens into that chamber. At the proximal and distal ends of chamber **303**, pair of dummy chambers **303***a*, **303***b* extend continuously with the main body of the chamber to form a single elongated cylindrical structure lying within the balloon **312**. However, the end chambers **303***a*, **303***b* are isolated from the injected coolant, and themselves form dummy spaces or uncooled regions that serve simply to provide positioning support. As further shown in FIG. **10**A, the balloon **312** has corresponding segments denoted **312***a*, **312***b* and **312***c* that are partitioned from each other such that the end segments are separated from the central cooling portion of the balloon. These segments lie over subchambers **303***a*, **303** and **303***b*. They may be serially connected or separately supplied with inflation material, so fluid entering the balloons is cooled only in the central region.

The illustrated embodiment of FIG. **10**A has a generally continuous balloon contour in which at least a portion of the end segments **312***a*, **312***b* inflates to the diameter of the surrounding blood vessel or tissue lumen and serves to displace blood, fluid or tissue away from the cryogenic treatment portion at the center of the catheter tip. As shown in FIG. **10**B, this has the effect of creating a cooling region that forms a relatively symmetrical ice ball volume (indicated by dashed lines in the Figure) around the vessel and catheter tip, with greater depth of penetration centered directly over the cryogenic chamber and with cooling damage tapering off away from that region. The balloon need not be a single continuous or partitioned balloon but may be implemented with separate balloons that in turn may be inflated via separate filler or inflation tubes (not illustrated) so as to more effectively achieve or more independently initiate the blocking and heat isolation functions. FIG. **10**C illustrates one such embodiment **400**, in which a cryogenic balloon **412** is surrounded by first and second blocking or blood displacing balloons **412***a*, **412***b* that are offset a short distance away from the ends of the coolant chamber. With this construction the excluding balloons may be positioned more remotely from the cryogenic segment.

In any of the foregoing embodiments, the balloon may be configured to apply a chilling level of cold without freezing or destroying tissue when appropriate for the tissue involved. As with the basic embodiment shown in FIGS. **8**A and **8**B, the catheter of the present invention preferably allows the withdrawal of sufficient thermal energy form the target site to freeze tissue, while the balloon anchors or enhances the positioning of the cryogenic source within the lumen so as to deploy the resulting ice ball in an appropriate relation to the surrounding tissue. The balloon enhances control of adjacent blood flow and may be used to arrest blood flow in the vessel entirely so that therapeutic cold accrues more quickly and is not dissipated. By actively pumping out the inflation fluid, collapse of the balloon following therapy allows more immediate resumption of circulation to perfuse tissue. Furthermore, by using a liquid-inflated balloon, the device may be deployed in much the same manner as an existing angioplasty catheter, and the guide wire lumen allows simple navigation and use of the device without requiring that the physician or cardiology specialist acquire additional operating skills or specialized training.

The catheter shaft may accommodate various lumens either as part of the shaft extrusion, or by carrying them as separate tubes such as an injection tube, a coolant exhaust lumen, a balloon inflation lumen, a guide wire lumen and other lumens, for example, for carrying wires to heating elements and/or monitoring devices to sense pressure, temperature and other sensing functions. By making the diameter of the cryogenic chamber large in relation to the targeted tissue lumen, the balloon may be formed with a low interior volume, facilitating the thawing of the inflation medium and reducing the time of total vascular obstruction. The thawing may further be advanced by providing and activating one or more heating elements, which may include any of a wide variety of heating means within the catheter body, such as resistive heating, radio frequency heating, laser heating applied via an optical fiber extending through the catheter body, microwave heating or heated gas or liquid infusion applied to the balloon portion. These may also include, in various treatment regimens, sources of energy that are externally applied to a catheter designed to preferentially receive such energy. Such external heating energy sources may, for example, be ultrasound or electromagnetic radiation applicators. The heater may also include various semiconductor, thin layer resistive or other similar technologies deployed, for example, on the balloon surface so as to heat one or more of the wall of the body lumen, the balloon inflation medium, or various pieces of the catheter structure.

In addition, the period of blood flow obstruction may be further reduced by providing a structure as shown in FIG. **11**. In this case, the catheter **500** includes perfusion channels **531**, **532** that extend through the catheter structure to allow blood to flow along the tissue lumen during the balloon inflation time interval and before extreme cooling has occurred to freeze off the central region. In this embodiment, the balloon may be inflated to securely position and center the assembly while blood continues to flow along the vessel. Cooling is then started. While the bypass channels **531**, **532** may be expected to freeze off once the cooling injection has started, the invention also contemplates that the bypass channels may be insulated from the cooling chamber, or they may include resistive or other heating elements to maintain their temperature suitable for continued blood flow during cryoablation. Such bypass passages may also be positioned in part in or through the catheter shaft or guide wire lumen.

The invention also contemplates a catheter as described above combined with other known catheter subassemblies or accessory devices such as drug delivery, energy delivery or

stent delivery elements, or structures for delivering radiation. In other embodiments the catheter may include one or more additional balloons such as a primary angioplasty balloon in addition to the blocking balloons and the cryotreatment balloon described above. In yet other embodiments of the invention, the catheter may include a supply tube for ejecting a bioactive or simply thermally conductive material in the space surrounding the cooling portion, to form a temporary frozen plug which may be left in place following withdrawal of the catheter.

FIGS. **12A** and **12B** illustrate two such delivery catheters **600**, **700**. As shown in FIG. **12A**, a first delivery catheter **600** includes an elongated body and cryogenic tip **610** with a cooling chamber **603** fed by a coolant injection lumen **601** as described above. Catheter **600** further carries a stent **620** on its outer surface and is configured to deliver and install the stent at an endoluminal site. By way of example the stent **620** is illustrated as having ends **621**, **622** contoured to retain the stent on the catheter during delivery, but other retention means, such as a removable or telescoping retaining sheath may be employed. The stent is made of a shape-memory alloy or other biphasic temperature-dependent material that changes its shape when brought to predetermined temperature. For operation, the catheter tip is deployed to a desired site and then operated to bring about a temperature-dependent change in shape or dimension of the stent **620**. This may be accomplished before, during, after, or independently of, the cryogenic treatment of nearby tissue. Depending on the particular alloy employed in stent **620**, the fixation in position and shape change may be effected by applying cryogenic temperature, or else a mild amount of cooling may be applied to cause the stent to retain a compact shape during insertion and the stent may subsequently deploy as the surrounding temperature rises to normal body temperature. It will be understood that in general the alloy properties of such materials may be adjusted so that a relatively large change in shape or conformation is achieved at one temperature threshold, which may be above or below body temperature. Accordingly, for this aspect of the invention, applicant contemplates the possibility of providing a heater as well as the cryochamber **603** to provide both hypo- and hyperthermal conditions to carry out stent deployment.

FIG. **12B** illustrates another embodiment **700** of a cryogenic delivery catheter of the invention. This embodiment again has the basic structure of a cooling chamber **703** in a distal cooling tip **710** fed by a coolant supply lumen **701**. However, in this embodiment an additional fluid delivery line **725** extends through the catheter body and is mounted to deliver fluid F externally of the tip **710** into the space between the cooling chamber exterior wall and the surrounding tissue. The delivery line **725** may have one or more outlets positioned to provide fluid F in defined locations. As illustrated in phantom by element **715**, a perforated membrane or other external distribution structure may also be provided to disperse or spread the fluid F exiting the delivery line **725**. In general, the delivery line **725** may deliver a therapeutic treatment liquid, or simply a heat conduction fluid to cryochamber surface. Applicant contemplates generally that during cryotreatment the fluid F will freeze in place, forming a plug that blocks flow, conducts thermal energy, and otherwise cooperates with the cryotreatment operation as described above. Advantageously, however, upon (or even prior to) completion of the freezing treatment, the catheter **700** may be withdrawn while leaving the frozen fluid mass in place. This mass then continues to chill the lumenal tissue wall, while (in the case of a vessel) circulation is immediately restored through the center. Thus, the duration of catheter freezing operation or the duration of blood flow occlusion may each be reduced, offering significant clinical advantages.

FIG. **13** illustrates yet another embodiment of the present invention, a dual balloon catheter system labeled generally as **800**. Catheter system **800** includes a catheter **805**, a handle unit **810**, a guidewire port **815**, a guidewire tube **820** enclosing a guidewire lumen **822**, a coolant port **825**, a coolant injection tube **830** enclosing a coolant injection lumen **835**, a vacuum port **840**, a vacuum return tube **845**, a primary vacuum return lumen **850**, a secondary vacuum return lumen **855**, an inner balloon **860**, an outer balloon **865**, a cooling chamber **870**, a proximal thermocouple **875**, a distal thermocouple **880**, and a distal tip **883**. The thermocouples may also be coupled to a temperature gauge **885** coupled to handle unit **810**.

The catheter **805** includes an elongate tube or series of tubes, conduits, flexible or rigid members generally suited for the flow of coolant therein, and for the insertion of such catheter into narrow body lumens such as blood vessels. Each of these tubes, conduits or members may include a number of lumens. As used herein, the term lumen refers not merely to the bore of a tube, but refers generally to a defined fluid pathway, suitable for the flow of coolant therethrough, connecting two or more spaces or elements such that the spaces or elements are in fluid communication. The catheter **805** is constructed similar to those embodiments previously discussed herein, and operates in a similar fashion so as to enable cryotreatment of tissue.

As shown in FIG. **13**, the catheter **805** is coupled to a handle unit **810** at its proximal end, and both of balloons **860** and **865** at its distal end. The handle unit **810** is fitted with multiple ports, including a guidewire port **815** for the insertion of a guidewire (not shown) into guidewire tube **820**. In addition, the handle unit **810** includes a coolant port **825** for the injection of coolant from a coolant supply (not shown) into coolant injection lumen **835**. The coolant injection lumen **835** is disposed between the coaxial coolant injection tube **830** disposed around guidewire tube **820**, as illustrated in FIG. **13**.

A vacuum port **840** is also coupled to the handle unit **810**, such port being coupled to a suitable vacuum generating device. A vacuum return tube **845** is disposed coaxially around the coolant injection tube **830** and inside of the catheter tube **805**. This creates two separate coaxial vacuum return lumens: a primary vacuum return lumen **850** disposed between coolant injection tube **830** and vacuum return tube **845**, and a secondary vacuum return lumen **855** disposed between the vacuum return tube **845** and the catheter body **805**.

FIG. **13A** illustrates a cross-section taken in the transverse direction of the catheter **805**, along lines A—A in FIG. **13**, showing the coaxial arrangement of the various tubes and lumens discussed above.

Turning back to FIG. **13**, the catheter **805** is coupled at its distal end to two balloons, inner balloon **860**, and outer balloon **865**. Each of these balloons include materials and are constructed in a manner similar to those balloons discussed in previous embodiments. The inner balloon **860** has an open proximal end coupled to the coaxial return tube **845**, and may have its lateral outer surface adhesively coupled to the guidewire tube **820**. The outer balloon **865** is disposed around the inner balloon **860**, having its proximal end coupled to the catheter tube **805** and its distal end coupled to the distal tip **883** disposed around the distal end portion of the guidewire lumen **822**.

High pressure coolant is injected through the coolant port **825** into the coolant injection lumen **835**, whereby it flows through such lumen to be injected into the inner balloon **860**. The inner balloon **860** thereby expands to create a cooling chamber **870** therein. The coolant then flows out of the cooling chamber **870** into the primary vacuum return lumen **850**, and eventually out of the device through the vacuum port **840**. For purposes of this invention, a "vacuum" is merely the effect of fluid evacuation, wherein static pressure in a space may be below that of atmospheric, or may be below the static pressure in the flow region immediately "upstream" of such space. Therefore, a "vacuum", as used herein, may refer simply to the existence of a negative pressure gradient in a flow region. Thus, the flow of coolant from the cooling chamber **870** through the primary vacuum return lumen **850** is driven by the negative pressure gradient created when the pressure therein is lower than the static pressure of coolant in the chamber **870**.

While the coolant is flowing through the chamber **870**, two thermocouples disposed therein may take temperature readings of the coolant, such temperature being measured by the temperature gauge **885**. While the proximal thermocouple **875** takes a temperature reading in the proximal section of the cooling chamber **870**, a distal thermocouple **880** takes a reading of coolant temperature in the distal section of cooling chamber **870**. As coolant is injected into the inner balloon **860**, the flow of coolant in such balloon is non-uniform, unsteady, and turbulent, such that a uniform temperature profile for cryotreatment is not achieved for a finite time. The thermocouples **875** and **880** provide for feedback control of the flow of coolant, and of the resultant temperature profile achieved in chamber **870**, thereby enabling more efficient cryotreatment.

FIG. **14** illustrates the distal end portion of the catheter system **800** of FIG. **13**. In addition to the elements displayed in FIG. **13**, FIG. **14** illustrates a coaxial coolant injection orifice **905**, an interstitial, "intra-balloon" space **910** disposed between inner balloon **860** and outer balloon **865**, and coolant flow lines F. Upon flowing through the coaxial injection tube **830**, coolant enters the chamber **870** through the injection orifice **905** located in the distal half of inner balloon **860**. Coolant thereafter generally flows in the direction F until the inner balloon **860** is inflated to form the cooling chamber **870** in substantially the shape and form shown in FIG. **14**. Coolant then flows out of the chamber **870** through the primary vacuum return lumen **850**.

While coolant is contained in the chamber **870**, the flow therein is regulated by the use of thermocouples **875** and **880**, so as to control the temperature profile therein. The pressure conditions inside of the chamber **870** may be regulated by controllably injecting the coolant through the orifice **905**, such that the desired mixture of liquid and gas phase coolant is evaporated and expanded, respectively, inside the chamber to achieve the desired cooling power. The injected coolant may be (i) substantially in gas phase immediately upon injection, thereby using mainly Joule-Thomson cooling to lower the temperature profile in the chamber **870**, or, (ii) substantially in liquid form, allowing for better control of temperature across the length of chamber **870**, while still providing cooling through the endothermic boiling of liquid phase coolant.

In either case, the pressure inside of the chamber **870** must be maintained at safe levels for insertion of the device into the human body. Generally, the static pressure of coolant inside of the chamber **870** must be maintained below 15 psia, or only slightly above the ambient pressure outside of the device. If a leak or rupture through the inner balloon **860** develops, the vacuum applied through the secondary vacuum return lumen **855** will act to siphon any leaking coolant from space **910** into the vacuum return lumen **855**. In this sense, the dual balloon configuration is robust with respect to balloon integrity failure, in that the failure of one balloon **860** is contained by the presence of another outer balloon **865**.

Furthermore, the presence of the space **910** provides additional thermal insulation which may be necessary when operating the device at relatively low pressure inside of chamber **870**. Empirical evidence shows that at chamber static pressures of 15 psia, the cooling power of the coolant flow expanding in the chamber **870** may at times be too high for safe and effective cryotreatment of adjacent tissue. In order to operate at such pressures, additional thermal resistance is needed around the inner balloon **860** to mitigate the excessive cooling power of the device. The space **910** effectively provides such insulation, which may be fine-tuned by applying varying levels of vacuum through the return lumen **855**. In such a manner, the effective temperature applied during cryotreatment of tissue may be warmer than that of the boiling temperature of the coolant.

However, FIG. **14** illustrates the disposition of the outer balloon **865** around the inner balloon **860** such that an interstitial envelope or space **910** exists therebetween, when inner balloon **860** is inflated to a pressure higher than that present in the secondary vacuum return lumen **855** and hence inside of the space **910**. This may be the case prior to the creation of vacuum pressure inside of the space **910**, as applied through the secondary vacuum return lumen **855**. However, once vacuum pressure is applied into the space **910**, the balloon configuration is that shown in FIG. **15**. Under such conditions, the space **910** is effectively of zero dimension along the lateral faces L of both balloons, such that the inner balloon **860** and the outer balloon **865** are in contact with one another along length L.

If the space **910** is thereby closed, the containment and insulating functions of the device are decreased. To counteract this, various methods and devices may be used to maintain the space **910** so as to enable vacuum containment of coolant leaks from, and provide additional thermal resistance around, the chamber **870**, while preventing the two balloons **860** and **865** from sealing in and apposing against each other as shown in FIG. **15**. The balloons **860** and **865** may still remain in apposition versus one another, but the space **910** will be maintained to achieve one of the purposes and functions of the present invention, as more specifically explained below.

One such embodiment is shown in FIG. **16A**, where the outer surface of inner balloon **860** is modified to create small surface patterns that extend from the outer surface as shown. As used herein, the term "surface modification" shall mean the creation or use of elements whose surfaces are topographically non-uniform, i.e. non-smooth. The slope at any point on such a surface may be continuous or non-continuous, but the surface itself will be continuous. These surface modifications **1010** may be achieved through conventional plasma treatment, vapor deposition, or through the use of electrically conductive or radiopaque materials as is known in the art, and may be patterned or non-patterned, so as to allow for more effective fluid pathways through the space **910**. Such surface modification thereby effectively maintains the space **910** at a finite level while vacuum is applied through the return lumen **855**.

Other configurations which maintain the space **910** are shown in FIGS. **16B** through **16E**. FIG. **16B** shows the use

of small particles **1020**, such as talcum powder, to be lodged in the space **910**. Alternatively, the space **910** could be filled with a fluid, which may itself be radiopaque or electrically conductive. In either case, the use of a vacuum return lumen coupled to the outer balloon **865** is not needed, and the outer balloon **865** is sealed to the coaxial vacuum return tube **845** which also serves as the outermost tube of the catheter shaft. This allows the particles **1020**, or fluid if fluid is used, to be sealed and contained in the space **1020** during operation of the device. Alternatively, a vacuum return tube such as is used in previous discussed embodiments may be coupled to the proximal end of balloon **865** and coupled with a separate injection mechanism (not shown) for maintaining the steady flow and presence of particles **1020**, or fluid, as needed, so as to maintain space **910** in its desired dimension.

FIG. **16**C shows the use of regular or irregularly patterned surface ridges **1030** coupled to either of: (i) the outer surface of inner balloon **860**, or (ii) the inner surface of outer balloon **865**. Another alternative to maintain space **910** is to use a braid or mesh type structure **1040** as shown in FIG. **16**D, wherein the mesh **1040** surrounds the outer surface of the inner balloon **860**. The cross-sectional thickness of the mesh **1040** provides for the thickness of the space **910**. The mesh **1040** may be a braid formed by a first group of flexible elongate elements **1042** helically wound in a first direction of rotation and a second group of flexible elements **1044** helically wound in a second direction of rotation to create a braid as shown in FIG. **16**D. The space **910** is thus maintained by the apposition of each of the inner balloon **860** and the outer balloon **865** against the mesh **1040**, wherein each flexible elongate element has a circular cross section defined by a diameter. In an exemplary embodiment, this diameter is in a range of approximately 0.001 to 0.010 inches. The flexible elongate elements **1042** and **1044** may be formed of metal, or a filament or fiber such as nylon, aramid, or polyester.

Finally, another embodiment uses a coil **1050** as shown in FIG. **16**E. Either of the coil or mesh may be made of metal, nylon, polyimide or other suitable material, as is known in the art. The coil **1050** may include a single element wound in a direction around the inner balloon **860**, or may be formed by a number of such elements wound in a parallel rotational direction so as to form a coil or spring. Each such coil element **1050** has a circular cross section defined by a diameter, wherein, in an exemplary embodiment, the diameter is in a range of approximately 0.001 to 0.010 inches. Alternatively, the coil element **1050** may have a rectangular cross section defined by a height vs. a width, wherein, in an exemplary embodiment, the height is in a range of approximately 0.001 to 0.010 inches, and the width is in a range of approximately 0.001 to 0.010 inches. The coil element **1050** may be formed of metal, or a filament or fiber such as nylon, aramid, or polyester.

The pressure conditions inside of the chamber **870** may also be monitored and regulated through the use of a pressure transducer **1060** located inside of the chamber **870**, as shown in FIG. **17**. The pressure transducer **1060** gives a user feedback control of the flow and pressure inside of the inner balloon **860** as the balloon is inflated and the catheter device is inserted and operated inside of a body lumen. Furthermore, the primary vacuum return lumen **850** may be set with a back pressure effective for inflating the cooling chamber **870** with the cooling fluid such that the cooling chamber **870** expands within a body lumen or vessel to position the device proximate to the vessel wall for performing cryotreatment. The back pressure is set to adjust the boiling temperature of the coolant and thereby determine the temperature applied to the surrounding tissue for cryotreatment. Such back pressure may be monitored and controlled by means of additional pressure transducers (not shown) in the catheter body. Furthermore, such a back pressure may be created by restricting the coolant return path through primary vacuum return lumen **850**. Such restriction may be created by selecting a diameter of either of the injection tube **830**, or coaxial return tube **845**, such that the coolant flow generates a residual pressure. Alternatively, the pressure conditions, including the chamber **870** pressure and the back pressure in return lumen **850**, may be regulated by the control of the coolant fluid flow rates.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described herein above. In addition, unless mention was made above to the contrary, it should be noted that all of the accompanying drawings are not to scale. A variety of modifications and variations are possible in light of the above teachings without departing from the scope and spirit of the invention, which is limited only by the following claims.

What is claimed is:

1. A catheter comprising:

an elongate catheter body,

a cooling chamber defined within the catheter body,

an expandable member disposed around the cooling chamber to define an interstitial space therebetween;

wherein the cooling chamber is a first expandable membrane inflatable from a first state to a second state;

wherein the catheter body further comprises a coolant injection tube in fluid communication with:

(i) a source of coolant, and

(ii) the cooling chamber,

and wherein the cooling chamber is inflatable by the flow of coolant from the injection tube into the first expandable membrane;

wherein the catheter body further comprises a primary coolant return lumen in fluid communication with:

(i) a source of fluid evacuation, and

(ii) the cooling chamber,

and wherein the coolant injection tube, the cooling chamber, and the primary coolant return lumen define a first fluid pathway for the flow of coolant; and

wherein the catheter body further comprises a secondary coolant return lumen in fluid communication with:

(i) a source of fluid evacuation, and

(ii) the interstitial space,

and wherein the interstitial space and the secondary coolant return lumen define a second fluid pathway for the flow of coolant.

2. The catheter of claim **1**, wherein the cooling chamber has an outer surface and the expandable member has an inner surface, said surfaces being substantially in apposition to one another to define a first volume of the interstitial space.

3. The catheter of claim **2**, wherein at least one of

(i) the inner surface of the expandable member, and

(ii) the outer surface of the cooling chamber,

is topographically non-uniform.

4. The catheter of claim **3**, wherein at least one of

(i) the inner surface of the expandable member, and

(ii) the outer surface of the cooling chamber,

is patterned to enhance the flow capacity of fluid flow in the interstitial space.

5. The catheter of claim 3, wherein at least one of

(i) the inner surface of the expandable member, and

(ii) the outer surface of the cooling chamber,

is in part formed using plasma treatment.

6. The catheter of claim 3, wherein at least one of

(i) the inner surface of the expandable member, and

(ii) the outer surface of the cooling chamber,

is in part formed using vapor deposition of additional material onto said surface.

7. The catheter of claim 3, wherein at least one of

(i) the inner surface of the expandable member, and

(ii) the outer surface of the cooling chamber,

is in part comprised of a plurality of partially raised surfaces arranged on said surface.

8. The catheter of claim 1, further comprising a plurality of small particles disposed in the interstitial space.

9. The catheter of claim 1, further comprising a flexible structure disposed within the interstitial space and around the cooling chamber.

10. The catheter of claim 7, wherein the flexible structure comprises at least one flexible elongate element wound in a first direction of rotation around the cooling chamber.

11. The catheter of claim 10, wherein the flexible structure further comprises at least one flexible elongate element wound in a second direction of rotation around the cooling chamber.

12. The catheter of claim 10, wherein the flexible elongate structure has a cross-sectional thickness in the range of 0.001 to 0.01 inches.

13. The catheter of claim 1, further comprising at least one temperature sensor disposed within the cooling chamber.

14. The catheter of claim 1, further comprising at least one pressure sensor disposed with the cooling chamber.

15. A catheter comprising:

a handle in fluid communication with

a supply of cooling fluid having a boiling temperature, and

a source of fluid evacuation,

a cooling chamber having fluid impermeable inner and outer surfaces,

an elongate catheter body having

a coolant injection lumen having proximal and distal end portions, the proximal end portion being in fluid communication with the supply of cooling fluid, the distal end portion being in fluid communication with the cooling chamber, and

a primary return lumen having proximal and distal end portions, the proximal end portion being in fluid communication with the source of vacuum, the distal end portion being in fluid communication with the cooling chamber,

an expandable member having inner and outer surfaces coupled around said cooling chamber, wherein a space exists between the cooling chamber outer surface and the expandable member inner surface, and

a secondary return lumen disposed within the catheter body, having proximal and distal end portions, the proximal end portion being in fluid communication with the source of vacuum, the distal end portion being in fluid communication with the space.

16. The catheter of claim 15, wherein the cooling chamber is controllably filled with cooling fluid, and vacuum is applied to the primary return lumen to direct the cooling fluid to flow from the cooling chamber through to the primary return lumen.

17. The catheter of claim 16, wherein the outer surface of the expandable member is disposed in contact with tissue proximate a body lumen to effect thermal conduction between said tissue and the flow of cooling fluid in the cooling chamber.

18. The catheter of claim 16, wherein vacuum is applied to the secondary return lumen.

19. The catheter of claim 15, wherein the cooling chamber is an inflatable membrane transitionable from a first volume to a second volume, the second volume being larger than the first volume.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 31292

ISTMT

DATE PRINTED
01/21/2011

CHRISTOPHER & WEISBERG, P.A.
200 EAST LAS OLAS BOULEVARD
SUITE 2040
FORT LAUDERDALE FL 33301

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,575,966	**$450.00**	**$0.00**	**11/09/06**	**09/945,319**	**06/10/03**	**08/31/01**	**04**	**NO**	**21819.00169**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 31292

ISTMT

DATE PRINTED
01/21/2011

CHRISTOPHER & WEISBERG, P.A.
200 EAST LAS OLAS BOULEVARD
SUITE 2040
FORT LAUDERDALE FL 33301

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,575,966	**$2,480.00**	**$0.00**	**10/11/10**	**09/945,319**	**06/10/03**	**08/31/01**	**08**	**NO**	**21819-169**

FAX COVER SHEET

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
OFFICE OF DEVICE EVALUATION

DIVISION OF CARDIOVASCULAR DEVICES
9200 CORPORATE BOULEVARD, HFZ-450
ROCKVILLE, MARYLAND 20850

NO. OF PAGES: 6 (including cover sheet) DATE: 8/29/3

TO: Flor del Pilar Arana FAX #:

COMMENTS:

G030159

SENDER'S NAME: Wil Ushenko

SENDER'S FAX#: ☐ (301) 594-3076 ☐ (301) 480-4204 ☐ (301) 827-4351
SENDER'S PHONE #: ☐ (301) 443-8320 ☐ (301) 443-8517 ☐ (301) 443-8262 ☐ (301) 443-8609 ☐ (301) 443-8243

FROM:
- ☐ Office of the Director
- ☐ Cardiac Electrophysiology & Monitoring Devices Branch (CEMB)
- ☐ Circulatory Support & Prosthetics Branch (CSPB)
- ☐ Interventional Cardiology Devices Branch (ICDB)
- ☐ Pacing, Defibrillator & Leads Branch (PDLB)
- ☐ Peripheral Vascular Devices Branch (PVDB)

PLEASE ADVISE IF TRANSMISSION IS ILLEGIBLE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 28 2003

Ms. Flor del Pilar Arana, MBA
Director Regulatory Affairs
CryoCath Technologies Inc.
16771 Chemin Ste-Marie Kirkland
Québec, Canada H9H 5H3

Re: G030159 and G030159/A001
7F Artic Circler CurviLinear Cardiac CryoAblation System
Indications for use: for cryablation of the conducting tissues in or near the os of the pulmonary veins (Arctic Circler™), the adjunctive cryoablation of linear lesion gaps in the pulmonary veins and any focal triggers (Freezor® Xtra), and the creation of a right atrial cavo-tricuspid isthmus cryoablation line (Freezor® MAX) in the treatment of patients with PAF.
Dated: July 30, 2003
Received: August 1, 2003
CMS Reimbursement Category: B4

Dear Ms. Arana:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application including the 7F Arctic Circler™, 7F Freezor® Xtra and 9F Freezor® MAX cryoablation catheters. Your application is conditionally approved, and you may begin your investigation at the institutions listed in the enclosure in accordance with the investigational site waiver granted below. Your investigation is limited to 3 institutions and 3 subjects.

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

Clinical

1. You have provided summary information from commercial experience with your device system in Europe. In 76 patients, there were reported 33 "technical issues". Please provide information about the nature of these issues and how they were mitigated. Have any of these issues required a catheter system redesign?

2. In the follow-up portion of your feasibility study, you have specified that all patients will get a MRI to evaluate pulmonary vein size at three months post ablation and then, if there is a "clinically significant change" in pulmonary vein size, they will get another MRI at 6 months. If this change has not occurred, they will not get another MRI until 12 months post ablation. Please provide a definition of "clinically significant." Also, please consider the use of a core laboratory for the evaluation of the MRIs.

3. One of the secondary endpoints for the feasibility study involves a reduction of symptomatic episodes from baseline to the 12 month follow-up. Please provide more information about how the baseline number of episodes will be confirmed. Please indicate the number of reduced episodes from baseline necessary for the patient to be considered a treatment success.

4. For clarity across centers, the FDA recommends providing a standard definition for the protocol of paroxysmal atrial fibrillation. For example, will the need for cardioversion make the atrial fibrillation classification be persistent?

5. One of the investigational catheters in your study will only be used for the cavo-tricuspid isthmus lesion. Please explain why the determination of bi-directional block is not to be considered in your effectiveness endpoint assessment.

6. Your protocol does not explicitly state which pulmonary veins are to be isolated or how the investigator makes this decision. The FDA fears that this inherent procedural variability will affect data analysis. Please specify how the investigators are to decide which pulmonary veins to isolate or justify why you do not believe that this will be a data analysis problem.

7. The FDA recommends that you review your case report forms in terms of how and where the investigator is to record the medicines that the patient is currently on at the time of the ablation procedure as opposed to the medicines that the patient has been on over their entire medical history. The form number six could be misconstrued and lead to inaccurate data recording.

Electrical Engineering

8. Please characterize the hazards involved in any pull forces being applied to the catheter during a cryoablation cycle for the Artic Circler, especially during pulmonary vein ablation where the cardiac tissue may be prone to mechanical damage.

9. Please characterize the temperature distribution along the circular catheter section of the Artic Circler during the cryoablation procedure. Also, please characterize the difference in temperature between the 0.005" "contact side" of the Pebax catheter jacket versus the 0.020" "non-contact side" of the Pebax catheter jacket.

Statistical

10. You indicate on Volume One, page 185 that the feasibility study results will be "compared to the FDA established OPC". Please note that the currently there is no OPC for atrial fibrillation and is not pertinent to this study per our discussion on August 28, 2003.

The conditions of approval identified above represent the issues that we believe need to be resolved before your IDE application can be fully approved. In developing the conditions of approval, we carefully considered the relevant statutory criteria for Agency decision-making as well as the burden that may be incurred in your attempt to respond to the conditions of approval. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

FDA will waive those requirements regarding the submission and prior FDA approval of a supplemental application and receipt of certification of institutional review board (IRB) approval for the addition of investigational sites (21 CFR 812.35(b)) provided:

1. The total number of investigational sites does not exceed 3.

2. You maintain current records on:

   a. the names and addresses of all investigational sites,
   b. the names and addresses of all investigators, identifying those that are currently participating,
   c. the names, addresses and chairpersons of all IRBs,
   d. the dates of the IRB approvals, and
   e. the dates of first shipment or first use of investigational devices for all participating institutions.

3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.

5. You submit to FDA, within 2 days of receipt of a request by FDA, a current list containing the information specified in 2(a-e) above.

6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent, that is, require any change which may increase the risks to subjects or affect the scientific soundness of the study. (Please note: If a significant change is requested, this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site.) Minor changes requested by the IRB may be made without prior FDA approval.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has approved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement. Please note, however, that you must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the limit specified above. Additionally, if you do not agree to these conditions, you must comply with the full requirements for the submission to FDA of a supplemental IDE application for new investigational sites not already specifically approved for participation in your study (21 CFR 812.35(b)).

We would like to point out that FDA approval of your IDE application does not imply that this investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597.

You should also give serious consideration to the following items which are considered essential for the analysis of your data for the purposes of determining safety and effectiveness for a future pivotal study and PMA application:

Future Pivotal Study Concern

1. As discussed in our conversation on August 28, 2003, you concurred that the effectiveness endpoints are not acceptable for a pivotal study. In order to obtain an approved PMA, the effectiveness endpoint is required to show clinical utility. The effectiveness endpoint for this

feasibility study does not show clinical utility and is not a recognized surrogate endpoint that can be used in the pivotal study. Please be aware that for the pivotal study, a clinically significant endpoint, i.e., an endpoint that will directly be useful to the individual patient, will be required for market approval of your device system. One of the secondary endpoints of the feasibility study could be an acceptable primary effectiveness endpoint for the pivotal study.

Future PMA Concern

2. Since the study will be using three different Cryoablation catheters, it will be necessary for you to either provide sufficient data to support the safety and effectiveness of each of the three different catheters by themselves or provide data to support marketing the catheters as a system.

3. Regression analysis might be used during data analysis to isolate device effect, which requires substantial amounts of data. Please consider the use of a randomized, controlled clinical trial in the pivotal study design, as randomization is the best assurance of comparable treatment and helps avoid confounding factors.

We have enclosed the guidance document entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Also enclosed is the guidance document "Investigators' Responsibilities for a Significant Risk Device Investigation" which you should provide to participating investigators.

Please note that the above conditions of approval should be satisfied within 45 days from the date of this letter or we may take steps to propose withdrawal of approval of your IDE application. If you have any questions, please contact Cindy Demian, M.S. at (301) 443-8517, ext. 172.

Sincerely yours,

Dina Kleiseher for

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures
(1) Sponsor's Responsibilities for a Significant Risk Device Investigation
(2) Investigators' Responsibilities for a Significant Risk Device Investigation

CCT S13
S1C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Flor del Pilar Arana
Director Regulatory Affairs
CryoCath Technologies Inc.
16771 Chemin Ste-Marie Kirkland
Québec, Canada H9H 5H3

MAY 25 2005

Re: G030159/S13 and S14
10F Arctic Circler Balloon Cardiac CryoAblation Catheter
Dated: May 5 and May 6, 2005
Received: May 6 and May 9, 2005

Dear Ms. Arana:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application. You have corrected the deficiencies cited in our March 15, 2005 conditional approval letter. Therefore, your supplements are approved and you may continue your investigation at the institutions enrolled in accordance with the investigational site waiver granted in our August 28, 2003 letter. Your investigation is limited to 4 institutions and 50 subjects.

If you have any questions, please contact Sabina Reilly at (301) 443-8320.

Sincerely yours,

for Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

March 12, 2010

CRYOCATH TECHNOLOGIES, INC.
C/O APPLIED PHYSICS
52 WEST BASIN RIDGE
GALISTEO, NEW MEXICO 87540
UNITED STATES
ATTN: FRED MILLER

Dear FRED MILLER:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA ORIGINAL. This PMA ORIGINAL has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P100010
Dated: 11-Mar-2010
Date Received: 12-Mar-2010
Device: ARCTIC FRONT CRYOCATHETER SYSTEM

Any questions concerning this submission should be directed to the PMA staff at (301)796-5640. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted to the PMA Document Mail Center (DMC,HFZ-401) at the above letterhead address.

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) and the FDA Amendments Act of 2007 (FDAAA), authorizes FDA to collect user fees for certain types of PMA submissions. Please visit our website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm for more information regarding fees and FDA review goals.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new section 402(j) (42 U.S.C. § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf) accompany 510(k)/HDE/PMA applications. The agency has issued a draft guidance titled: "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007" (http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm). According to the draft guidance, certain device applications to the FDA that are not related to clinical trials do not need the certification form.

We also remind you that Title III of FDAAA, section 515A(a)(2) of the Act, requires HDE applications, or PMA/PDP applications (or supplements to PMA/PDP applications) to include the following information: (1) a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and (2)the number of affected pediatric patients.

In future premarket submissions, we encourage you to provide (or continue to provide) an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's eCopies Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm.

Sincerely yours,

Senora F. Smallwood
Consumer Affairs Specialist
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Chronology of Events on Arctic Front® CryoAblation Catheter System

IDE G030159
PMA P100010

The table below lists all communication with FDA during Arctic Front cryoballoon review from the IDE submission to the final PMA approval –

Definitions: ACL Arctic Circler Linear cryoablation catheter
ACB: Arctic Circler Balloon catheter
AR: Annual Report

Date	To FDA	From FDA	Summary
04 June 2003	x		I020095 Pre IDE meeting on Arctic Circler Linear cryoablation system
30 July 2003	x		IDE Feasibility study submission (PS-009) including ACL/Freezor MAX and Freezor Xtra catheters
28 August 2003		x	G030159 Conditional approval letter to initiate clinical investigations limited to 3 institutions and 30 patients –
14 October 2003	x		G030159 Response to FDA letter dated 28 August 2003
13 November 2003	x		**5 Day Notice** – Protocol Change: use of RF energy to complete the ablation lesion of Cavo-tricuspid isthmus
14 November 2003		x	G030159 AI requested letter from FDA: same conditions of approval (3 institutions and 30 subjects)
17 December 2003		x	G030159 Acknowledgement letter for protocol change
22 December 2003	x		G030159 Response to FDA letter dated 14 November 2003
22 January 2004		x	G030159 Acknowledgement letter, all deficiencies have been corrected
27 February 2004	x		G030159 6 month progress report
30 March 2004	x		**5 day notice** Catheter component design change
30 July 2004	x		**5- day notice** Catheter's handle improvement
20 September 2004	x		I040413 Pre IDE meeting for Pivotal study initiation – new catheter to be used Arctic Circler Balloon
12 October 2004	x		G030159 Annual progress report (2004)

Date	To FDA	From FDA	Summary
15 October 2004	x		G030159 Feasibility study submission with ACB catheter and Freezor MAX catheter (PS012)
22 October 2004	x		Minutes of the pre-IDE meeting
17 November 2004		x	G030159 FDA disapproval letter
09 December 2004	x		G030159 First Response to FDA letter dated 17 November 2004
12 January 2005		x	G030159 FDA disapproval letter and request for additional information on several deficiencies
11 February 2005	x		G030159 Second Response to FDA letter dated 17 November 2004
15 March 2005		x	G030159 FDA conditionally approval letter: 3 institutions and 50 subjects
28 March 2005	x		G030159 Addition of a new institution (site#4)
13 April 2005		x	G030159 FDA approval letter for 4 sites and 50 subjects
05 May 2005	x		G030159 Request for fully approval of the IDE
25 May 2005		x	G030159 IDE full approval granted
31 May 2005	x		**5-day notice:** Withdrawal of ACL and addition of FlexCath Steerable sheath and changes to protocol
30 June 2005		x	G030159 FDA letter converted to 5-day notice to IDE supplement and conditionally approved the submission
19 July 2005	x		**5 day notice:** Changes to the protocol (include pacemaker patients into the study)
01 August 2005	x		G030159 Compassionate use request
01 August 2005	x		G030159 First Response to FDA letter dated 30 June 2005
08 August 2005		x	G030159 FDA approval for protocol change
10 August 2005		x	G030159 FDA approval for compassionate use of ACB
28 August 2005	x		G030159 Annual Progress report and 6 month progress report (2005)
01 September 2005		x	G030159 FDA conditional approval letter, AI required
20-21 September 2005		x	G030159 Acknowledgement message from FDA

Date	To FDA	From FDA	Summary
11 October 2005	x		G030159 30 June 2005 Second Response to FDA letter dated 30 June 2005
24 October 2005	x		G030159 Pivotal study submission: Arctic Front catheter with new balloon size (28mm) - (PS-023)
04 November 2005		x	G030159 All deficiencies from FDA letter 01 September 2005 were addressed- Full approval granted
23 November 2005		x	G030159 FDA disapproval letter and request for AI
20 December 2005	x		**5-day notice** First Response to FDA letter dated 23 November 2005
22 December 2005	x		G030159 Request to approve a live case using balloon catheter
04 January 2006	x		**5-day notice** Addition of two AF sizes in feasibility study
06 January 2006	x		G030159 Second Response to FDA letter dated 23 November 2005
09 January 2006		x	G030159 FDA approval to perform the live case demonstration
31 January 2006		x	G030159 FDA approval letter for 5 day notification submission
02 February 2006		x	G030159 FDA disapproval letter and request for AI
13 March 2006	x		G030159 Design and Protocol changes
13 April 2006		x	G030159 FDA approval letter (4 sites & 57 subjects)
08 June 2006	x		**5-day notice** Manufacturing improvement
02 August 2006	x		G030159 Response to deficiencies in FDA letter dated 02 February 2006
24 August 2006	x		G030159 Annual Progress report and 6 month progress report (2006)
31 August 2006		x	G030159 FDA conditional approval letter and request for AI (5 sites & 132 subjects)
18 October 2006	x		G030159 Request for an extension of time to respond to FDA conditional approval letter
26 October 2006	x		G030159 Response to FDA letter dated 31 August 2006
22 November 2006		x	G030159 FDA conditional approval letter and request for AI (20 sites & 207 subjects)

Date	To FDA	From FDA	Summary
21 December 2006	x		G030159 Request for an extension of time to respond to the FDA conditional approval letter dated 22 November 2006
05 January 2007		x	G030159 FDA approval for additional 30 days to respond to deficiencies
07 February 2007	x		G030159 Compassionate use request
16 February 2007	x		G030159 Response to deficiencies in FDA letter dated 22 November 2006
08 March 2007		x	G030159 Compassionate use approval by FDA
13 March 2007	x		G030159 Recall notification of FlexCath® sheath
22 March 2007		x	G030159 FDA conditional approval letter – suspension of enrollment (20 sites & 327 subjects)
23 March 2007	x		G030159 Additional information on FlexCath removal
20 April 2007		x	G030159 FDA conditional approval letter and request for AI (20 sites & 327 subjects)
27 April 2007	x		**5-day notice** Devices manufacturing improvement
08 May 2007	x		Request for an extension of time to respond to the FDA conditional approval letter dated 22 March 2007
29 May 2007	x		G030159 Response to FDA letter dated 22 March 2007 and 20 April 2007
29 June 2007		x	G030159 FDA conditional approval letter (20 sites & 327 subjects)
23 July 2007	x		G030159 Response to FDA letter dated 29 June 2007 (25 sites & 327 subjects)
27 July 2007	x		G030159 Request to increase the number of sites
21 August 2007		x	G030159 FDA full approval letter (25 sites and 327 subjects)
28 August 2007	x		**5-day notice** FlexCath Packaging improvement
30 August 2007	x		G030159 Annual Progress report (2007)
04 October 2007		x	G030159 Request for additional information by FDA on AR
30 October 2007	x		G030159 Protocol changes

Date	To FDA	From FDA	Summary
20 November 2007	x		G030159 Response to FDA letter dated 04 October 2007
30 November 2007		x	G030159 FDA approved 2 out of 3 protocol changes
12 December 2007	x		**5-day notice** Revised version of the protocol
12 December 2007	x		G030159 Compassionate use request
21 December 2007		x	G030159 Compassionate use approval by FDA
11 January 2008		x	G030159 FDA conditional approval letter for protocol changes
17 January 2008	x		G030159 Response to FDA letter dated 11 January 08
12 February 2008		x	G030159 FDA approval granted for the revised protocol
18 February 2008	x		G030159 Request for shelf life extension
19 February 2008		x	G030159 Conditional approval letter and request for AI on CAP
20 March 2008		x	G030159 FDA disapproval letter and request for AI
20 March 2008	x		PMA shell and Modular Plan submission: Module I: June 2008; Module II September 2008; Module III December 2008 and Module IV June 2009
28 March 2008		x	M080006 FDA acknowledgement letter
6 May 2008			**5-day notice** Removal of FlexCath sheath
28 May 2008	x		G030159 Response to FDA letter dated 20 March 2008
29 May 2008	x		M080006 Request to modify the PMA shell
26 June 2008		x	G030159 FDA approval granted for shelf life extension
10 July 2008	x		G030159 Major Design change to catheter and Cryoconsole
30 July 2008	x		M080006 Bench Testing/Design Module 1 submission
30 July 2008		x	M080006 FDA acknowledgment letter
08 August 2008		x	G030159 FDA disapproval letter and request for AI
15 August 2008	x		G030159 Compassionate use request
28 August 2008	x		G030159 Annual Progress Report (2008)

Date	To FDA	From FDA	Summary
03 September 2008	x		G030159 Response to FDA letter dated 08 August 2008
12 September 2008		x	G030159 Compassionate use approval by FDA
30 September 2008	x		M080006 Animal studies Module 2 submission
01 October 2008		x	G030159 FDA letter requesting additional information on AR
03 October 2008		x	G030159 FDA approval granted for major changes
29 October 2008	x		G030159 Response to FDA letter dated 01 October 2008
03 November 2008	x		G030159 Application proposing a Continued Access Protocol study (CAP)
07 November 2008		x	M080006 FDA letter with deficiencies on Module 1
26 November 2008		x	G030159 FDA letter requesting additional information on AR
04 December 2008		x	G030159 FDA conditional approval letter and request for AI on CAP study
15 December 2008	x		Request modification to PMA shell- Change Module III submission date from December 2008 to March 2009
29 December 2008		x	M080006 FDA letter with deficiencies on Module 2
08 January 2009	x		G030159 Response to FDA letter dated 26 November 2008
16 & 19 January 2009	x		G030159 Response to FDA letter dated 04 December 2008 (CAP study)
06 February 2009		x	G030159 FDA letter requesting additional information on AR
23 February 2009	x		G030159 Response to FDA letter dated 06 February 2009
12 March 2009		x	G030159 FDA letter requesting additional information on AR
25 March 2009	x		M080006 Response to FDA letter dated 07 November 2008
21 April 2009		x	G030159 FDA approval letter for CAP study (12 sites and 100 subjects)
23 April 2009	x		G030159 Response to FDA letter dated 12 March 2009
04 May 2009	x		M080006 Response to FDA letter dated 29 December 2008
21 May 2009		x	G030159 FDA letter requesting additional information on AR

Date	To FDA	From FDA	Summary
29 May 2009	x		M080006 Manufacturing information Module 3 submission
24 June 2009		x	M080006 FDA request for additional information
06 July 2009	x		G030159 Response to FDA letter dated 21 May 2009
08 July 2009		x	G030159 FDA acknowledgement letter
28 July 2009		x	M080006 FDA letter closing Module 2
19 August 2009		x	M080006 FDA letter with deficiencies on Module 3
07 September 2009	x		G030159 Annual Progress report (2009)
08 October 2009		x	G030159 FDA letter requesting additional information on AR
20 October 2009	x		M080006 Response to FDA letter dated 24 June 2009
21 October 2009		x	M080006 FDA acknowledgment letter
30 October 2009	x		M080006 Response to Deficiencies letter dated 19 August 2009
19 November 2009	x		G030159 Response to FDA letter dated 08 October 2009 (AR)
23 November 2009		x	G030159 FDA acknowledgement letter
07 December 2009		x	M080006 FDA's e-mail requesting clarification
07 December 2009	x		M080006 Response to FDA e-mail dated 07 December 2009
09 December 2009		x	M080006 FDA acknowledgment letter
14 December 2009		x	G030159 FDA letter approval for AR
22 December 2009		x	M080006 FDA letter closing Module 1
16 February 2010	x		**5-day notice** New adhesive on catheter connector
18 February 2010		x	M080006 FDA letter closing Module3
22 February 2010		x	G030159 FDA acknowledgement letter
11 March 2010	x		M080006 Clinical study Module 4 submission - Final PMA
12 March 2010		x	P100010 FDA acknowledgment letter for Final PMA
22 April 2010	x		**5- day notice** Protocol amendment on PNP patients

Date	To FDA	From FDA	Summary
23 April 2010		x	G030159 FDA acknowledgement letter
03 June 2010		x	P100010 FDA Fillable letter
15 June 2010	x		P100010 Day-100 meeting Request
16 June 2010	x		P100010 Manufacturing change-New Warehouse
22 June 2010	x		P100010 No Panel rationale submission
22 July 2010		x	P100010 FDA Major Deficiencies letter
27 August 2010	x		G030159 Annual Progress report (2010)
02 September 2010	x		P100010 Response to FDA letter dated 22 June 2010
29 September 2010		x	G030159 FDA letter requesting additional information on AR
07 October 2010		x	P100010 FDA 2nd Deficiencies letter
11 November 2010	x		G030159 Response to FDA letter dated 29 September 2010
02 December 2010	x		P100010 Response to FDA letter dated 07 October 2010
17 December 2010		x	P100010 Arctic Front System PMA approval letter
20 December 2010	x		P100010 Final device labeling

1318494v1